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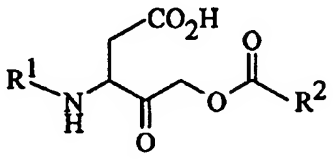
(54) Title: ASPARTATE ESTER INHIBITORS OF INTERLEUKIN-1β CONVERTING ENZYME



(I)

(57) Abstract

The present invention relates to compounds that are inhibitors of interleukin-1β converting enzyme that have formula (I). This invention also relates to a method of treatment of stroke, inflammatory diseases, reperfusion injury, Alzheimer's disease, and shigellosis, and to a pharmaceutically acceptable composition that contains a compound that is an inhibitor of interleukin-1β converting enzyme.

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ASPARATE ESTER INHIBITORS OF INTERLEUKIN-1β CONVERTING ENZYME

FIELD OF THE INVENTION

This invention relates to compounds that are inhibitors of interleukin-1β converting enzyme. This invention also relates to a method of treatment of stroke, reperfusion injury, Alzheimer's disease, shigellosis, inflammatory diseases, and to a pharmaceutically acceptable composition that contains a compound that is an inhibitor of interleukin-1β converting enzyme.

BACKGROUND OF THE INVENTION

The compounds of the present invention are inhibitors of interleukin-1β converting enzyme (ICE; Caspase-1) and are useful in treating diseases in which interleukin-1 plays a role.

ICE acts on pro-interleukin-1β (pro-IL-1β) to produce interleukin-1β (IL-1β), which is an inflammatory cytokine. In addition, ICE (Caspase-1) regulates at least four cytokines. ICE activates IL-β and IL-18 and indirectly regulates the production of IL-1∝ and IFNγ. Several diseases are associated with interleukin-1 activity. Examples of diseases in which interleukin-1 is involved include, but are not limited to, inflammatory diseases such as rheumatoid arthritis and inflammatory bowel disease, neuroinflammatory disorders such as stroke. Other diseases include septic shock, reperfusion injury, Alzheimer's disease, and shigellosis.

Agents that modulate IL-1β activity have been shown to have beneficial in vivo effects. For example, compounds that are interleukin-1 receptor antagonists have been shown to inhibit ischaemic and excitotoxic damage in rat brains. See, for example, Relton J.K., et al., Brain Research Bulletin, 1992;29:243-246. Additionally, ICE inhibitors were shown to reduce

inflammation and pyrexia in rats. See Elford P.R., et al., British Journal of Pharmacology, 1995;115:601-606.

The compounds of the present invention are also inhibitors of other cysteine proteases in the ICE family. Many of these proteases have only recently been described in the literature. While the nomenclature is still unresolved, the following proteases are representative members of this class of enzymes; Ich-2 (also called Tx or ICErel-II), ICErel-III, Ich-I (also called Nedd-2), CPP-32 (also called apopain and yama), Mch-2, Mch-3 (also called ICE-lap3, CMH-1), and Ced-3. See Henkart P.A., Immunity, 1996;4:195-201. It is recognized that members of this enzyme family play key biological roles in both inflammation and apoptosis (programmed cell death). In particular, Caspase-4 can activate IL-1β and IL-18. It has been shown that a murine homolog of Caspase-4 can activate ICE. Thus, inhibition of Caspase-4 will act to inhibit ICE. See Thornberry N.A., et al., Perspectives in Drug Discovery and Design, 1994;2:389-399.

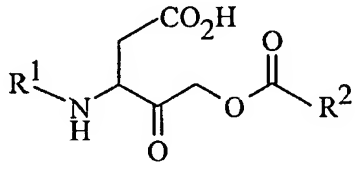
In addition to its effects on IL-1β production, ICE has been shown to play a role in the production of the inflammatory mediator interferon-γ (Ghayur, et al., Nature, 1997;386(6625):619-623). ICE processes the inactive proform of interferon-γ inducing factor (IGIF; Interleukin-18) to active IGIF, a protein which induces production of interferon-γ by T-cells and natural killer cells. Interferon-γ has been implicated in the pathogenesis of diseases such as inflammatory disorders and septic shock. Therefore, ICE inhibitors would be expected to have beneficial effects in such disease states by effects on interferon-γ.

Recently, the nomenclature of those cysteine proteases in the ICE family (also known as caspases with ICE being known as Caspase-1) has been further defined. The following proteases are representative members of this class of enzymes using the nomenclature described in Alnemri, et al, Cell, 1996;87:171: Caspase-2 (also known as Ich-1); Caspase-3 (also known as CPP32, Yama, and apopain); Caspase-4 (also known as TX, Ich-2, and ICE rel-II); Caspase-5 (also known as ICE rel-III); Caspase-6 (also known as Mch2); Caspase-7 (also known

as Mch3); Caspase-8 (also known as FLICE and Mch5); Caspase-9 (also known as ICE-LAP6 and Mch6); Caspase-10 (also known as Mch4).

SUMMARY OF THE INVENTION

The present invention provides compounds of the Formula I



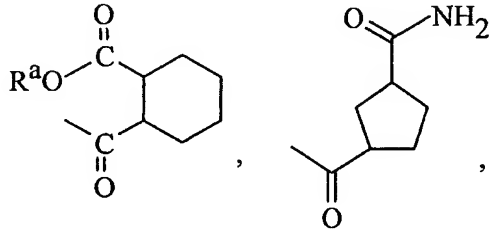
I

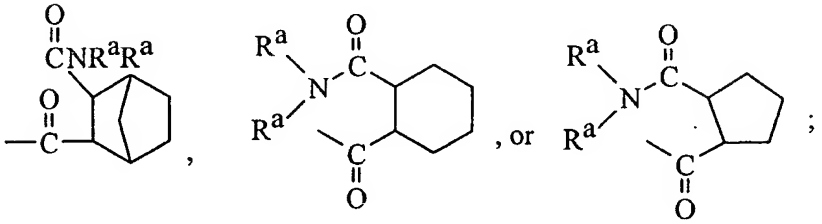
wherein R^1 is $R^3OC(=O)$-,

R^3CO-,

R^3SO_2-,

R^5NCHR^6CO-,





each R^a is independently hydrogen, C_1-C_6 alkyl, or $-(CH_2)_n$ aryl;

R^2 is $-(CRR)_n$-aryl,

-$(CRR)_n$-X-aryl,

-$(CRR)_n$-heteroaryl,

-$(CRR)_n$-X-heteroaryl,

-$(CRR)_n$-(substituted-heteroaryl),

-$(CRR)_n$-(substituted-aryl),

-$(CRR)_n$-X-(substituted-aryl),

-$(CRR)_n$-aryl-aryl,

-$(CRR)_n$-aryl-heteroaryl,

-$(CRR)_n$-aryl-$(CH_2)_n$-aryl,

-$(CRR)_n$-$CH(aryl)_2$,

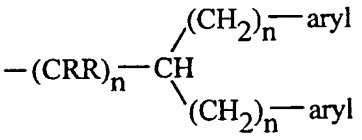
-$(CRR)_n$-cycloalkyl,

-$(CRR)_n$-X-cycloalkyl,

-$(CRR)_n$-heterocycle,

-$(CRR)_n$-X-heterocycle,

-$(CRR)_n$ substituted heterocycle,



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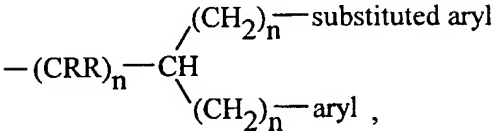

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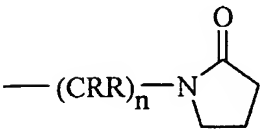

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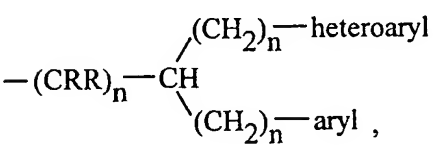

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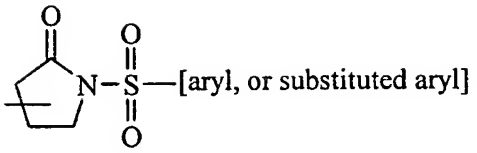
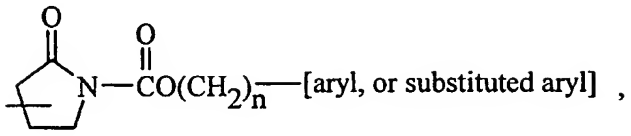
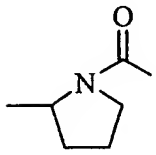
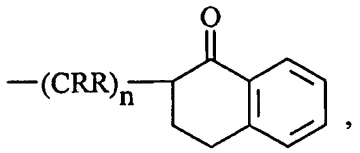
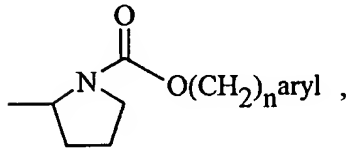
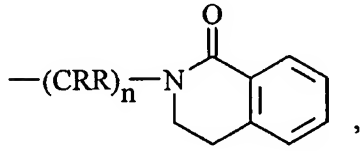

O
O
N–S—[aryl, or substituted aryl]
O
,

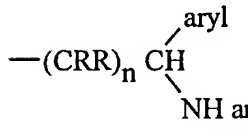

O
O
N—CO(CH2)n—[aryl, or substituted aryl]
,

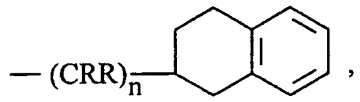

O
N
aryl
,

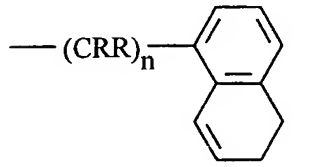

O
—(CRR)n
,

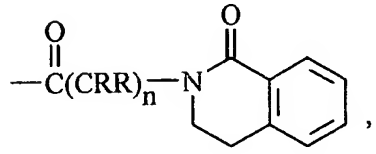

O
N
O(CH2)naryl
,

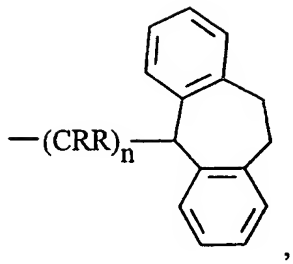

O
—(CRR)n—N
,


aryl
—(CRR)n CH
NH aryl
,


— (CRR)n
,


— (CRR)n
,


O
O
—C(CRR)n—N
,



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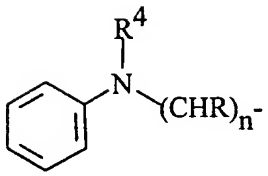

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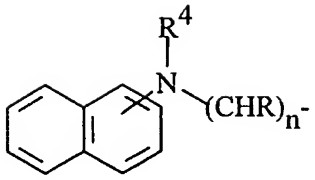


;

each R is independently hydrogen, C_1-C_6 alkyl, halogen or hydroxy;

X is O or S;

R^3 is C_1-C_6 alkyl,

aryl,

heteroaryl,

-$(CHR)_n$-aryl,

-$(CHR)_n$-heteroaryl,

-$(CHR)_n$-substituted heteroaryl,

-$(CHR)_n$-substituted aryl,

-$(CRR)_n$$COR^a$,

-$(CRR)_n$$S(CH_2)_n$-aryl,

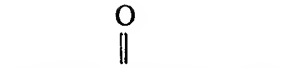
cycloalkyl,

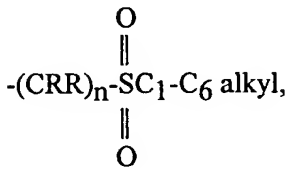
substituted cycloalkyl,

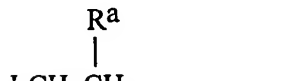
heterocycle,

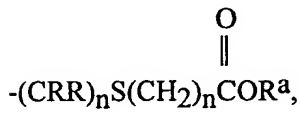
substituted heterocycle,

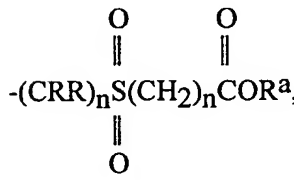
-$(CRR)_n$$CNR^aR^a$,

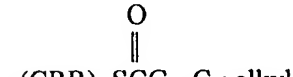


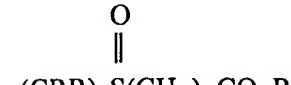


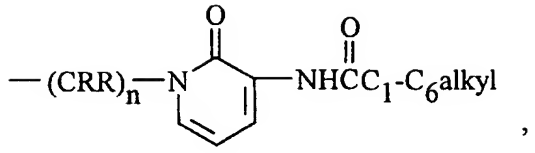












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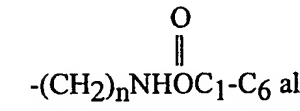

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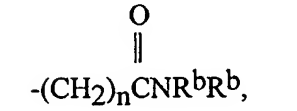

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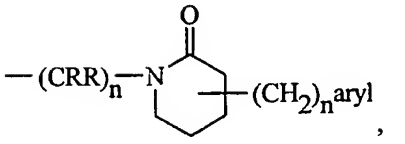

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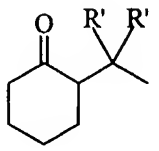

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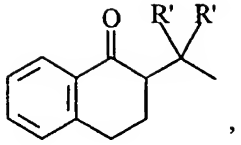

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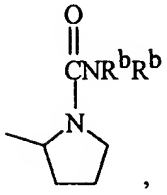

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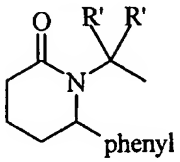

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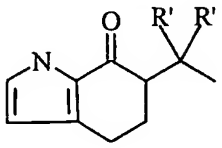

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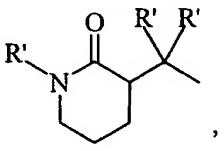

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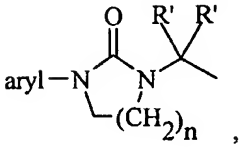

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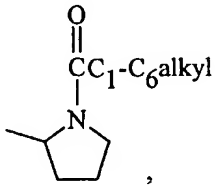

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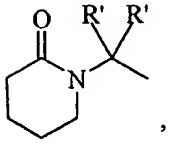

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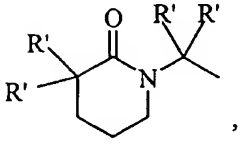

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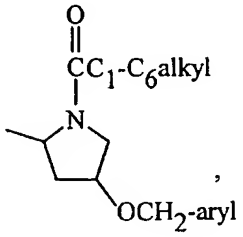

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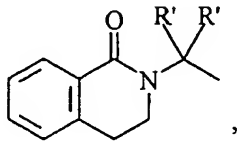

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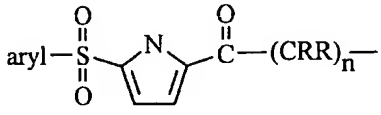

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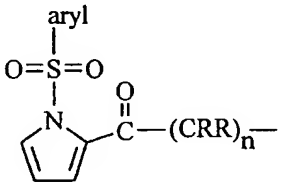


each R′ is independently C_1-C_6 alkyl,

C_1-C_6 alkylaryl,

aryl, or

hydrogen;

each J is independently

$-CO_2R^b$,

$-CONR^bR^b$,

$-SO_2NR^bR^b$, or

$-SO_2R^b$;

each R^b is independently hydrogen, C_1-C_6 alkyl, aryl, substituted aryl;

arylalkyl, heteroarylalkyl, substituted arylalkyl, or substituted heteroarylalkyl;

R^4 is hydrogen,

C_1-C_6 alkyl,

$CH_3OC(=O)-$,

-phenyl, or

C_1-C_6 alkyl $C(=O)-$;

R^5 is C_1-C_6 alkyl-CO-,

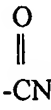
$-(CH_2)_n$ aryl,

C_1-C_6-alkyl$OC(=O)-$,

C_1-C_6-alkyl-X-$(CH_2)_nCO$,

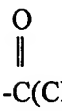
C_1-C_6-alkyl-X-$(CH_2)_nOC(=O)-$,

$-C(CRR)_n$aryl,



$-CNR^aR^a$,

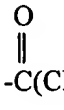
$-SC_1$-C_6 alkyl,



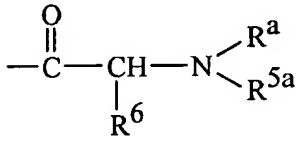
$-C(CH_2)_nCNR^aR^a$,

$-CO(CH_2)_n$ aryl,

$-CO(CH_2)_n$ substituted aryl,



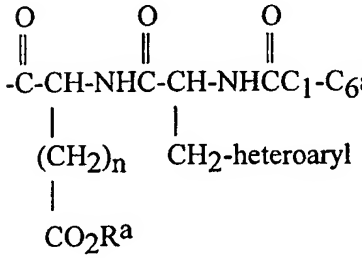
$-C(CRR)_nNHCO(CH_2)_n$-aryl,



,

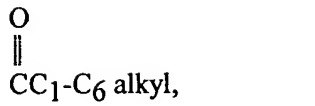
$-(CH_2)_nX(CH_2)_n$-aryl,

$-C_1$-C_6 alkyl X-C_1-C_6 alkyl aryl, or

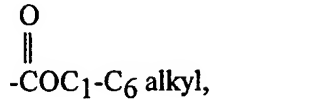


$-C(CH(CH_2)_nCO_2R^a)NHC(CH_2\text{-heteroaryl})NHCC_1$-$C_6$alkyl;

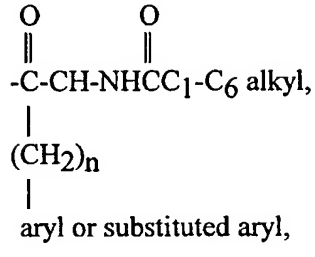
R^{5a} is



CC_1-C_6 alkyl,



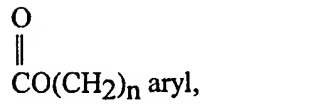
-COC_1-C_6 alkyl,



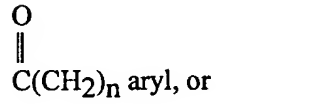
-C-CH-NHCC_1-C_6 alkyl,

$(CH_2)_n$

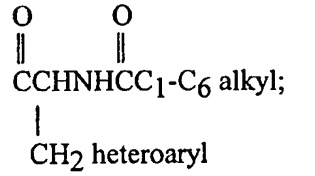
aryl or substituted aryl,



$CO(CH_2)_n$ aryl,



$C(CH_2)_n$ aryl, or



CCHNHCC_1-C_6 alkyl;

CH_2 heteroaryl

R^6 is hydrogen,

C_1-C_6 alkyl, -$(CH_2)_n$ aryl, -$(CH_2)_nCO_2R^a$, hydroxyl substituted C_1-C_6 alkyl, or imidazole substituted C_1-C_6 alkyl;

each n is independently 0 to 3, and the pharmaceutically acceptable, salts, esters, amides, and prodrugs thereof.

In a preferred embodiment of the compounds of Formula I, R^1 is

phenyl-CH_2-OC-.

In another preferred embodiment of the compounds of Formula I, R^1 is phenyl-SO_2-.

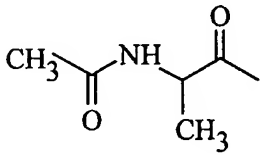
In another preferred embodiment of the compounds of Formula I,

R^1 is CH_3-OC-.

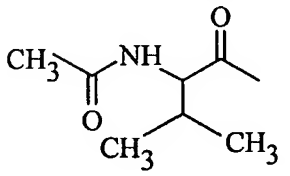
In another preferred embodiment of the compounds of Formula I,

R^1 is phenyl-CH_2CH_2-CO-.

In another preferred embodiment of the compounds of Formula I,

R^1 is  .

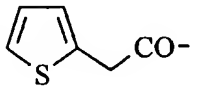
In another preferred embodiment of the compounds of Formula I,

R^1 is  .

In another preferred embodiment of the compounds of Formula I,

R^1 is phenyl-CH_2-CO-.

In another preferred embodiment of the compounds of Formula I,

R^1 is  .

In another preferred embodiment of the compounds of Formula I,

R^a is hydrogen.

In another preferred embodiment of the compounds of Formula I,

R^2 is -$(CH_2)_n$-phenyl.

In another preferred embodiment of the compounds of Formula I,

R^2 is -$(CH_2)_n$-naphthyl.

In another preferred embodiment of the compounds of Formula I,

R^2 is -$(CH_2)_n$-O-phenyl.

In another preferred embodiment of the compounds of Formula I,

R^2 is -$(CH_2)_n$-O-naphthyl.

In another preferred embodiment of the compounds of Formula I,

R^2 is $-(CH_2)_n$-S-phenyl.

In another preferred embodiment of the compounds of Formula I,

R^2 is-$(CH_2)_n$-CH(phenyl)$_2$.

In another preferred embodiment of the compounds of Formula I,

R^a is hydrogen; R^1 is benzyloxycarbonyl; R^2 is aryl-$X(CRR)_n$-, aryl-$(CRR)_n$-, heteroaryl-$(CRR)_n$-, or cycloalkyl-$(CRR)_n$-; n is 1, 2, or 3; X is O or S; and R is hydrogen, methyl, or benzyl.

In another preferred embodiment of the compounds of Formula I,

R^a is hydrogen;

R^1 is benzyloxycarbonyl; and

R^2 is $-(CH_2)_n$-naphthyl,

$-(CH_2)_n$-phenyl,

$-(CH_2)_n$-cycloalkyl,

$-(CH_2)_nO(CH_2)_n$-naphthyl,

$-(CH_2)_nO(CH_2)_n$-phenyl, or

$-(CH_2)_nS(CH_2)_n$-phenyl.

In another preferred embodiment of the compounds of Formula I,

R^a is hydrogen;

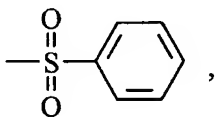
R^1 is benzyloxycarbonyl; and

R^2 is $-CH_2$-naphthyl.

In another preferred embodiment of the compounds of Formula I,

R^a is hydrogen;

R^2 is benzyloxycarbonyl,



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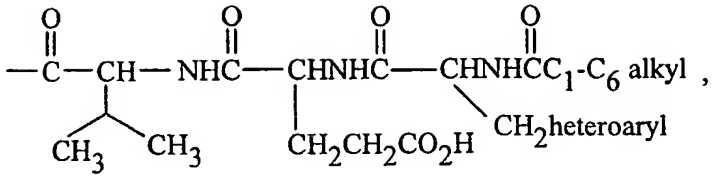
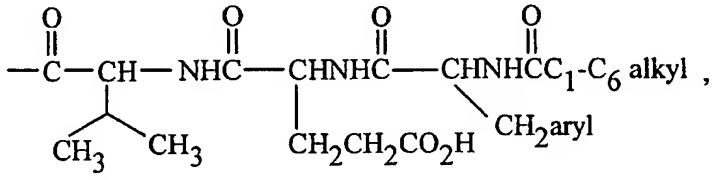
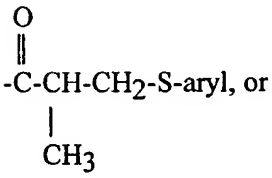
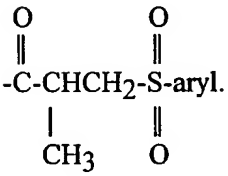








Also provided is a method of inhibiting interleukin-1β converting enzyme, the method comprising administering to a patient in need of inhibition of interleukin-1β converting enzyme a therapeutically effective amount of a compound of Formula I.

Also provided is a method of inhibiting Caspase-4, the method comprising administering to a patient in need of Caspase-4 inhibition a Caspase-4 inhibiting amount of a compound of Formula I.

Also provided is a method of treating stroke, the method comprising administering to a patient having a stroke or having had a stroke a therapeutically effective amount of a compound of Formula I.

Also provided is a method of treating inflammatory diseases, the method comprising administering to a patient having an inflammatory disease a therapeutically effective amount of a compound of Formula I.

In a preferred embodiment of the treatment of inflammatory diseases, the inflammatory disease is arthritis.

In a preferred embodiment of the treatment of inflammatory diseases, the inflammatory disease inflammatory bowel disease.

Also provided is a method of treating reperfusion injury, the method of comprising administering to a patient having reperfusion injury a therapeutically effective amount of a compound of Formula I.

Also provided is a method of treating Alzheimer's disease, the method comprising administering to a patient having Alzheimer's disease a therapeutically effective amount of a compound of Formula I.

Also provided is a method of treating shigellosis, the method comprising administering to a patient having shigellosis a therapeutically effective amount of a compound of Formula I.

Also provided is a pharmaceutically acceptable composition that contains a compound of Formula I.

Also provided are the compounds:

3-Benzyloxycarbonylamino-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid;

3-Benzyloxycarbonylamino-4-oxo-5-(3-phenyl-propionyloxy)-pentanoic acid;

3-Benzyloxycarbonylamino-5-(3-cyclohexyl-propionyloxy)-4-oxo-pentanoic acid;

3-Benzyloxycarbonylamino-5-[(naphthalene-1-yl-oxy)-acetoxy]-4-oxo-pentanoic acid;

3-Benzyloxycarbonylamino-4-oxo-5-phenoxyacetoxy-pentanoic acid;

3-Benzyloxycarbonylamino-4-oxo-5-phenylsulfanylacetoxy-pentanoic acid;

3-Benzyloxycarbonylamino-5-[(6-methoxy-naphthalene-1-yl)-acetoxy]-4-oxo-pentanoic acid;

3-Benzyloxycarbonylamino-5-(naphthalene-2-yl-acetoxy)-4-oxo-pentanoic acid;

3-Benzyloxycarbonylamino-5-(3-naphthalene-2-yl-propionyloxy)-4-oxo-pentanoic acid;

3-Benzyloxycarbonylamino-5-(3,3-diphenyl-propionyloxy)-4-oxo-pentanoic acid;

3-Benzyloxycarbonylamino-5-[(1H-indol-3-yl)-acetoxy]-4-oxo-pentanoic acid;

3-Benzyloxycarbonylamino-5-(indol-1-yl-acetoxy)-4-oxo-pentanoic acid;

3-Benzyloxycarbonylamino-5-(2-naphthalene-1-yl-propionyloxy)-4-oxo-pentanoic acid;

3-Benzyloxycarbonylamino-4-oxo-5-[(2-oxo-pyrrolidin-1-yl)-acetoxy]-pentanoic acid;

5-[(Acetyl-phenyl-amino)-acetoxy]-3-benzyloxycarbonyl-amino-4-oxo-pentanoic acid;

3-Benzyloxycarbonylamino-5-(2-benzyl-3-phenyl-propionyloxy)-4-oxo-pentanoic acid;

3-Benzyloxycarbonylamino-5-(hydroxy-naphthalene-1-yl-acetoxy)-4-oxo-pentanoic acid;

3-Benzyloxycarbonylamino-4-oxo-5-[(phenyl-amino)-acetoxy]-pentanoic acid;

3-Benzyloxycarbonylamino-5-[(6-hydroxy-naphthalene-1-yl)-acetoxy]-4-oxo-pentanoic acid;

3-Benzyloxycarbonylamino-5-[3-(4-hydroxy-phenyl)-2-naphthalene-1-yl-propionyloxy)-4-oxo-pentanoic acid;

(S)-3-Benzyloxycarbonylamino-4-oxo-5-phenylacetoxy-pentanoic acid;

(S)-3-Benzyloxycarbonylamino-4-oxo-5-(4-phenyl-butyryloxy)-pentanoic acid;

3-Benzyloxycarbonylamino-4-oxo-5-[(4-phenyl-naphthalen-1-yl)-acetoxy]-pentanoic acid;

3-Benzyloxycarbonylamino-5-[(4-methyl-naphthalen-1-yl)-acetoxy]-4-oxo-pentanoic acid;

3-Benzyloxycarbonylamino-4-oxo-5-[(4-thiophen-2-yl-naphthalen-1-yl)-acetoxy]-pentanoic acid;

3-Benzyloxycarbonylamino-5-[(4-fluoro-naphthalen-1-yl)-acetoxy]-4-oxo-pentanoic acid;

3-Benzyloxycarbonylamino-5-[(2-methyl-naphthalen-1-yl)-acetoxy]-4-oxo-pentanoic acid;

3-Benzyloxycarbonylamino-5-[(2-fluoro-naphthalen-1-yl)-acetoxy]-4-oxo-pentanoic acid;

5-(Benzofuran-4-yl-acetoxy)-3-benzyloxycarbonylamino-4-oxo-pentanoic acid;

5-(Benzo[b]thiophen-7-yl-acetoxy)-3-benzyloxycarbonylamino-4-oxo-pentanoic acid;

5-(Benzo[b]thiophen-4-yl-acetoxy)-3-benzyloxycarbonylamino-4-oxo-pentanoic acid;

5-[(4-Benzyl-naphthalen-1-yl)-acetoxy]-3-benzyloxycarbonylamino-4-oxo-pentanoic acid;

3-Benzyloxycarbonylamino-5-[(3,4-dihydro-naphthalen-1-yl)-acetoxy]-4-oxo-pentanoic acid;

3-Benzyloxycarbonylamino-5-[(5-bromo-1H-indol-3-yl)-acetoxy]-4-oxo-pentanoic acid;

3-Benzyloxycarbonylamino-5-(3,4-diphenyl-butyryloxy)-4-oxo-pentanoic acid;

3-Benzyloxycarbonylamino-4-oxo-5-(3-phenyl-3-phenylamino-propionyloxy)-pentanoic acid;

3-Benzyloxycarbonylamino-4-oxo-5-[(1,2,3,4-tetrahydro-naphthalen-2-yl)-acetoxy]-pentanoic acid;

3-Benzyloxycarbonylamino-5-[(1-methanesulfonyl-piperidin-4-yl)-acetoxy]-4-oxo-pentanoic acid;

3-Benzyloxycarbonylamino-4-oxo-5-[(2,3,5,6-tetramethyl-phenyl)-acetoxy]-pentanoic acid;

5-(Benzothiazol-4-yl-acetoxy)-3-benzyloxycarbonylamino-4-oxo-pentanoic acid;

5-(Benzofuran-3-yl-acetoxy)-3-benzyloxycarbonylamino-4-oxo-pentanoic acid;

5-(Benzo[b]thiophen-3-yl-acetoxy)-3-benzyloxycarbonylamino-4-oxo-pentanoic acid;

3-Benzyloxycarbonylamino-4-oxo-5-(3-phenyl-3-pyridin-2-yl-propionyloxy)-pentanoic acid;

3-Benzyloxycarbonylamino-5-[(2,3-dichloro-phenyl)-acetoxy]-4-oxo-pentanoic acid;

3-Benzyloxycarbonylamino-5-[(5-methyl-naphthalen-1-yl)-acetoxy]-4-oxo-pentanoic acid;

3-Benzyloxycarbonylamino-5-[(2-iodo-phenyl)-acetoxy]-4-oxo-pentanoic acid;

3-Benzyloxycarbonylamino-4-oxo-5-(3-pyridin-3-yl-propionyloxy)-pentanoic acid;

3-Benzyloxycarbonylamino-5-[(5-methoxy-naphthalen-1-yl)-acetoxy]-4-oxo-pentanoic acid;

3-Benzyloxycarbonylamino-5-[(8-methyl-naphthalen-1-yl)-acetoxy]-4-oxo-pentanoic acid;

3-Benzyloxycarbonylamino-5-[(9H-fluoren-9-yl)-acetoxy]-4-oxo-pentanoic acid;

3-Benzyloxycarbonylamino-5-[(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-acetoxy]-4-oxo-pentanoic acid;

5-Oxo-1-(toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid 3-benzyloxycarbonylamino-4-carboxy-2-oxo-butyl ester;

5-Oxo-pyrrolidine-1,2-dicarboxylic acid 1-benzyl ester 2-(3-benzyloxycarbonylamino-4-carboxy-2-oxo-butyl) ester;

1-Benzoyl-pyrrolidine-2-carboxylic acid 3-benzyloxycarbonylamino-4-carboxy-2-oxo-butyl ester;

Pyrrolidine-1,2-dicarboxylic acid 1-benzyl ester 2-(3-benzyloxycarbonylamino-4-carboxy-2-oxo-butyl) ester;

3-Benzyloxycarbonylamino-5-(2-benzyl-3-phenyl-propionyloxy)-4-oxo-pentanoic acid;

3-Benzyloxycarbonylamino-5-[(5-cyano-naphthalen-1-yl)-acetoxy]-4-oxo-pentanoic acid;

3-Benzyloxycarbonylamino-4-oxo-5-(3-phenyl-3-pyridin-3-yl-propionyloxy)-pentanoic acid;

3-Benzyloxycarbonylamino-4-oxo-5-(3-phenyl-3-pyridin-4-yl-propionyloxy)-pentanoic acid; and

3-Benzyloxycarbonylamino-4-oxo-5-[(1-oxo-3,4-dihydro-1H-isoquinolin-2-yl)-acetoxy]-pentanoic acid.

Also provided are the compounds:

3-Benzenesulfonylamino-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid;

3-Methoxycarbonylamino-5-(naphthalene-1-yl-acetoxy)-4-oxo-pentanoic acid;

5-(Naphthalene-1-yl-acetoxy)-4-oxo-3-(3-phenyl-propionylamino)-pentanoic acid;

3-Methoxycarbonylamino-4-oxo-5-phenoxyacetoxy-pentanoic acid; and

3-(2-Methanesulfonyl-1-methyl-ethylsulfanylamino)-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid.

Also provided are the compounds:

[S-(R*,R*)]-3-(2-Acetylamino-propionylamino)-5-(naphthalene-1-yl-acetoxy)-4-oxo-pentanoic acid;

5-(Naphthalen-1-yl-acetoxy)-4-oxo-3-[(thiophene-3-carbonyl)-amino]-pentanoic acid;

3-[(Furan-3-carbonyl)-amino]-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid;

5-(Naphthalen-1-yl-acetoxy)-4-oxo-3-[2-(4-phenyl-butyrylamino)-propylamino]-pentanoic acid;

3-(2-Methanesulfonylamino-propionylamino)-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid;

3-[2-(2-Acetylamino-4-phenyl-butyrylamino)-propionylamino]-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid;

3-(2-Acetylamino-butyrylamino)-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid;

3-[2-(4-Carbamoyl-butyrylamino)-propionylamino]-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid;

3-(2-Benzyloxycarbonylamino-propionylamino)-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid;

5-(Naphthalen-1-yl-acetoxy)-4-oxo-3-(2-ureido-propionylamino)-pentanoic acid;

3-(2-Acetylamino-propionylamino)-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid;

3-[(1-Acetyl-pyrrolidine-2-carbonyl)-amino]-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid;

3-(2-Methyl-3-oxo-3-thiophen-2-yl-propionylamino)-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid;

3-(2-Acetylamino-acetylamino)-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid;

3-(2-Acetylamino-propionylamino)-5-(3,3-diphenyl-propionyloxy)-4-oxo-pentanoic acid;

3-[2-(2-Acetylamino-4-carboxy-butyrylamino)-propionylamino]-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid;

5-(Naphthalen-1-yl-acetoxy)-4-oxo-3-[2-(3-phenyl-propionylamino)-propionylamino]-pentanoic acid;

3-[2-(3-Methyl-butyrylamino)-propionylamino]-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid;

3-[(1-Acetyl-4-benzyloxy-pyrrolidine-2-carbonyl)-amino]-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid;

3-(4-Carbamoyl-butyrylamino)-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid; and

3-[2-(1-Methyl-1H-imidazol-4-yl)-acetylamino]-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid.

Also provided are the compounds:

(S)-5-(Naphthalene-1-yl-acetoxy)-4-oxo-3-phenylacetylamino-pentanoic acid;

(S)-5-(Naphthalene-1-yl-acetoxy)-4-oxo-3-(2-thiophene-2-yl-acetylamino)-pentanoic acid;

3-[(2-Carbamoyl-cyclopentanecarbonyl)-amino]-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid;

3-[(3-Carbamoyl-bicyclo[2.2.1]heptane-2-carbonyl)-amino]-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid;

3-(3-Methanesulfonyl-2-methyl-propionylamino)-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid;

3-(3-Benzenesulfonyl-2-methyl-propionylamino)-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid;

3-Butyrylamino-5-(naphthalen-2-yl-acetoxy)-4-oxo-pentanoic acid;

3-Acetylamino-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid;

3-(3-Methanesulfonyl-2-methyl-propionylamino)-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid;

3-(3-Methyl-butyrylamino)-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid;

3-(3-Carbamoyl-propionylamino)-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid;

[S-(R*,R*)]-3-(3-Acetylsulfanyl-2-methyl-propionylamino)-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid; and

trans-3-[(3-Carbamoyl-cyclopentanecarbonyl)-amino]-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid.

Also provided are the compounds:

3-(1,2,3,4-tetrahydro-1-oxo-isoquinoline-2-yl)-acetamino-5-(naphthalene-1-yl acetoxy)-4-oxo-pentanoic acid;

3-(2-Methyl-3-phenethylcarbamoyl-propionylamino)-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid;

5-(Naphthalen-2-yl-acetoxy)-4-oxo-3-[2-(2-oxo-6-phenyl-piperidin-1-yl)-acetylamino]-pentanoic acid;

5-(Naphthalen-1-yl-acetoxy)-4-oxo-3-[2-(2-oxo-6-phenyl-piperidin-1-yl)-acetylamino]-pentanoic acid;

3-[3-Methyl-2-(3-phenyl-propionylamino)-butyrylamino]-4-oxo-5-[(1-oxo-1,2,3,4-tetrahydro-naphthalen-2-yl)-acetoxy]-pentanoic acid;

3-(Naphthalen-2-yl-acetoxy)-4-oxo-3-[2-(1-oxo-3,4-dihydro-1H-isoquinolin-2-yl)-acetylamino]-pentanoic acid;

5-(2-Benzyl-3-phenyl-propionyloxy)-4-oxo-3-[2-(1-oxo-3,4-dihydro-1H-isoquinolin-2-yl)-acetylamino]-pentanoic acid;

5-(2-Benzyl-3-phenyl-propionyloxy)-4-oxo-3-[2-(2-oxo-6-phenyl-piperidin-1-yl)-acetylamino]-pentanoic acid;

5-(Naphthalen-1-yl-acetoxy)-4-oxo-3-[2-(1-oxo-1,2,3,4-tetrahydro-naphthalen-2-yl)-acetylamino]-pentanoic acid;

5-(Naphthalen-1-yl-acetoxy)-4-oxo-3-[2-(1-oxo-3,4-dihydro-1H-isoquinolin-2-yl)-propionylamino]-pentanoic acid;

5-(Naphthalen-2-yl-acetoxy)-4-oxo-3-[2-(1-oxo-3,4-dihydro-1H-isoquinolin-2-yl)-propionylamino]-pentanoic acid;

3-[4-(1-Benzenesulfonyl-1H-pyrrol-2-yl)-4-oxo-butyrylamino]-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid;

5-(2-Benzyl-3-phenyl-propionyloxy)-4-oxo-3-[2-(1-oxo-1,2,3,4-tetrahydro-naphthalen-2-yl)-acetylamino]-pentanoic acid;

5-(2-Benzyl-3-phenyl-propionyloxy)-4-oxo-3-[2-(1-oxo-3,4-dihydro-1H-isoquinolin-2-yl)-propionylamino]-pentanoic acid;

4-Oxo-3-[2-(1-oxo-3,4-dihydro-1H-isoquinolin-2-yl)-propionylamino]-5-[(1-oxo-1,2,3,4-tetrahydro-naphthalen-2-yl)-acetoxy]-pentanoic acid;

3-[4-(1-Benzenesulfonyl-1H-pyrrol-2-yl)-4-oxo-butyrylamino]-5-(2-benzyl-3-phenyl-propionyloxy)-4-oxo-pentanoic acid;

4-Oxo-5-[(1-oxo-1,2,3,4-tetrahydro-naphthalen-2-yl)-acetoxy]-3-[2-(1-oxo-1,2,3,4-tetrahydro-naphthalen-2-yl)-acetylamino]-pentanoic acid;

5-(Naphthalen-1-yl-acetoxy)-4-oxo-3-[2-(2-oxo-3-phenyl-imidazolidin-1-yl)-propionylamino]-pentanoic acid;

5-(Naphthalen-1-yl-acetoxy)-4-oxo-3-[2-(2-oxo-3-phenyl-tetrahydro-pyrimidin-1-yl)-propionylamino]-pentanoic acid;

5-(Naphthalen-1-yl-acetoxy)-4-oxo-3-[2-(2-oxo-3-phenyl-tetrahydro-pyrimidin-1-yl)-acetylamino]-pentanoic acid;

3-(2-Acetylamino-3-methyl-butyrylamino)-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid;

3-(2-Acetylamino-3-methyl-butyrylamino)-5-(2-benzyl-3-phenyl-propionyloxy)-4-oxo-pentanoic acid;

3-(2-Acetylamino-3-methyl-butyrylamino)-5-(3-benzyl-4-phenyl-butyryloxy)-4-oxo-pentanoic acid;

3-(2-Acetylamino-3-methyl-butyrylamino)-5-(4-benzyl-5-phenyl-pentanoyloxy)-4-oxo-pentanoic acid;

3-(2-Acetylamino-3-methyl-butyrylamino)-4-oxo-5-[(1-oxo-1,2,3,4-tetrahydro-naphthalen-2-yl)-acetoxy]-pentanoic acid;

5-(3-Benzyl-4-phenyl-butyryloxy)-3-[3-methyl-2-(3-phenyl-propionylamino)-butyrylamino]-4-oxo-pentanoic acid;

3-[2-(3-Acetylamino-2-oxo-2H-pyridin-1-yl)-acetylamino]-5-(3,3-diphenyl-propionyloxy)-4-oxo-pentanoic acid; and

3-[2-(3-Acetylamino-2-oxo-2H-pyridin-1-yl)-acetylamino]-5-(2-benzyl-3-phenyl-propionyloxy)-4-oxo-pentanoic acid.

Also provided are the compounds:

3-[2-(2-Benzyloxycarbonylamino-4-carboxy-butyrylamino)-3-methyl-butyrylamino]-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid;

3-[2-(2-Benzyloxycarbonylamino-3-methyl-butyrylamino)-propionylamino]-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid;

3-(2-Acetylamino-3-methyl-butyrylamino)-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid;

3-[2-(2-Benzyloxycarbonylamino-3-methyl-butyrylamino)-propionylamino]-5-(3,3-diphenyl-propionyloxy)-4-oxo-pentanoic acid;

3-[2-(2-Benzyloxycarbonylamino-3-methyl-butyrylamino)-propionylamino]-5-(2-benzyl-3-phenyl-propionyloxy)-4-oxo-pentanoic acid;

3-[2-(2-Benzyloxycarbonylamino-3-methyl-butyrylamino)-propionylamino]-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid;

5-(2-Benzyl-3-phenyl-propionyloxy)-3-{2-[4-carboxy-2-(3-phenyl-propionylamino)-butyrylamino]-3-methyl-butyrylamino}-4-oxo-pentanoic acid;

3-(2-Benzyloxycarbonylamino-3-methyl-butyrylamino)-5-(3,3-diphenyl-propionyloxy)-4-oxo-pentanoic acid;

3-(2-Acetylamino-3-hydroxy-butyrylamino)-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid;

3-(2-Acetylamino-3-hydroxy-butyrylamino)-5-(3,3-diphenyl-propionyloxy)-4-oxo-pentanoic acid;

3-(2-{2-[2-Acetylamino-3-(1H-indol-3-yl)-propionylamino]-4-carboxy-butyrylamino}-3-methyl-butyrylamino)-5-(2-benzyl-3-phenyl-propionyloxy)-4-oxo-pentanoic acid; and

5-(3,3-Diphenyl-propionyloxy)-4-oxo-3-[2-(4-phenyl-butyrylamino)-propionylamino]-pentanoic acid.

Also provided are the compounds:

3-(2-{2-[2-Acetylamino-3-(1H-indol-3-yl)-propionylamino]-4-carboxy-butyrylamino}-3-methyl-butyrylamino)-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid; and

3-(2-{2-[2-Acetylamino-3-(4-hydroxy-phenyl)-propionylamino]-4-carboxy-butyrylamino}-3-methyl-butyrylamino)-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid.

Also provided are the compounds:

3-[(2-Carboxy-cyclohexanecarbonyl)-amino]-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid;

3-[(2-Methoxycarbonyl-cyclohexanecarbonyl)-amino]-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid; and

3-[(2-Carbamoyl-cyclohexanecarbonyl)-amino]-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid.

Also provided are the compounds:

3-(3-Benzylsulfanyl-2-methyl-propionylamino)-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid;

3-(2-Methyl-3-phenylmethanesulfonyl-propionylamino)-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid;

3-[3-(2-Carboxy-ethanesulfanyl)-2-methyl-propionylamino]-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid;

5-(2-Benzyl-3-phenyl-propionyloxy)-3-[3-(2-carboxy-ethanesulfonyl)-2-methyl-propionylamino]-4-oxo-pentanoic acid;

5-(2-Benzyl-3-phenyl-propionyloxy)-3-[3-(3-carboxy-propane-1-sulfinyl)-2-methyl-propionylamino]-4-oxo-pentanoic acid;

5-(Naphthalen-1-yl-acetoxy)-4-oxo-3-(2-phenylmethanesulfanyl-propionylamino)-pentanoic acid;

3-(2-Methyl-3-phenylsulfanyl-propionylamino)-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid;

5-(2-Benzyl-3-phenyl-propionyloxy)-3-(2-methyl-3-phenylsulfanyl-propionylamino)-4-oxo-pentanoic acid;

3-(2-Methyl-3-phenethylsulfanyl-propionylamino)-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid;

5-(2-Benzyl-3-phenyl-propionyloxy)-3-(2-methyl-3-phenethylsulfanyl-propionylamino)-4-oxo-pentanoic acid;

5-(2-Benzyl-3-phenyl-propionyloxy)-3-(3-benzylsulfanyl-2-methyl-propionylamino)-4-oxo-pentanoic acid;

5-(2-Benzyl-3-phenyl-propionyloxy)-3-(2-benzylsulfanyl-propionylamino)-4-oxo-pentanoic acid;

3-[2-Methyl-3-(3-phenyl-propylsulfanyl)-propionylamino]-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid;

3-(3-Benzenesulfonyl-2-methyl-propionylamino)-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid;

3-(3-Benzenesulfonyl-2-methyl-propionylamino)-5-(2-benzyl-3-phenyl-propionyloxy)-4-oxo-pentanoic acid;

5-(2-Benzyl-3-phenyl-propionyloxy)-3-[2-methyl-3-(2-phenyl-ethanesulfonyl)-propionylamino]-4-oxo-pentanoic acid;

3-[2-Methyl-3-(2-phenyl-ethanesulfonyl)-propionylamino]-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid;

5-(Naphthalen-1-yl-acetoxy)-4-oxo-3-(2-phenylmethanesulfonyl-propionylamino)-pentanoic acid;

5-(2-Benzyl-3-phenyl-propionyloxy)-3-(2-methyl-3-phenylmethanesulfonyl-propionylamino)-4-oxo-pentanoic acid;

5-(2-Benzyl-3-phenyl-propionyloxy)-4-oxo-3-(2-phenylmethanesulfonyl-propionylamino)-pentanoic acid;

3-[2-Methyl-3-(3-phenyl-propane-1-sulfonyl)-propionylamino]-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid;

5-(2-Benzyl-3-phenyl-propionyloxy)-3-[2-methyl-3-(3-phenyl-propane-1-sulfonyl)-propionylamino]-4-oxo-pentanoic acid;

5-(2-Benzyl-3-phenyl-propionyloxy)-3-[3-(2-carboxy-ethylsulfanyl)-2-methyl-propionylamino]-4-oxo-pentanoic acid;

3-[3-(3-Carboxy-propylsulfanyl)-2-methyl-propionylamino]-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid;

5-(2-Benzyl-3-phenyl-propionyloxy)-3-[3-(3-carboxy-propylsulfanyl)-2-methyl-propionylamino]-4-oxo-pentanoic acid;

3-(3-Carboxymethylsulfanyl-2-methyl-propionylamino)-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid;

5-(2-Benzyl-3-phenyl-propionyloxy)-3-(3-carboxymethylsulfanyl-2-methyl-propionylamino)-4-oxo-pentanoic acid;

3-[3-(2-Carboxy-ethanesulfonyl)-2-methyl-propionylamino]-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid;

3-[3-(3-Carboxy-propane-1-sulfonyl)-2-methyl-propionylamino]-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid;

3-(3-Carboxymethanesulfonyl-2-methyl-propionylamino)-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid;

5-(2-Benzyl-3-phenyl-propionyloxy)-3-[3-(3-carboxy-propane-1-sulfonyl)-2-methyl-propionylamino]-4-oxo-pentanoic acid;

5-(2-Benzyl-3-phenyl-propionyloxy)-3-(3-carboxymethanesulfonyl-2-methyl-propionylamino)-4-oxo-pentanoic acid;

3-[3-(3-Carboxy-propane-1-sulfinyl)-2-methyl-propionylamino]-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid;

3-[2-Methyl-3-(3-phenyl-propane-1-sulfinyl)-propionylamino]-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid; and

5-(2-Benzyl-3-phenyl-propionyloxy)-3-[2-methyl-3-(3-phenyl-propane-1-sulfinyl)-propionylamino]-4-oxo-pentanoic acid.

Also provided are the compounds:

3-[3-Methyl-2-(phenethylcarbamoyl-methyl)-butyrylamino]-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid; and

3-(3-Carboxy-2-methyl-propionylamino)-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid.

Also provided is the compound:

3-(2-Methyl-3-sulfamoyl-propionylamino)-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid.

Also provided are the compounds:

3-(3-Carbamoyl-2-methyl-propionylamino)-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid;

3-(2-Benzyloxycarbonylamino-3-methyl-naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid;

3-[(2-Carbamoyl-cyclopentanecarbonyl)-amino]-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid;

3-[(1-Carbamoyl-pyrrolidine-2-carbonyl)-amino]-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid;

3-(2-{2-[2-Acetylamino-3-(4-hydroxy-phenyl)-propionylamino]-4-carboxy-butyrylamino}-3-methyl-butyrylamino)-5-(2-benzyl-3-phenyl-propionyloxy)-4-oxo-pentanoic acid;

3-(3-Carbamoyl-2-methyl-propionylamino)-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid;

3-(2-Carbamoylmethyl-3-methyl-butyrylamino)-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid;

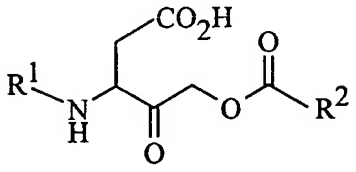
3-(3-Benzyloxy-2-ureido-propionylamino)-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid;

3-[2-(2-Benzyloxycarbonylamino-4-carboxy-butyrylamino)-3-methyl-butyrylamino]-5-(2-benzyl-3-phenyl-propionyloxy)-4-oxo-pentanoic acid;

3-{2-[4-Carboxy-2-(3-phenyl-propionylamino)-butyrylamino]-3-methyl-butyrylamino}-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid; and

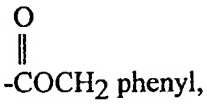
3-[2-(2-Acetylamino-4-carboxy-butyrylamino)-3-methyl-butyrylamino]-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid.

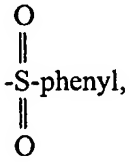
Also provided are compounds of the Formula I

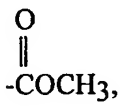


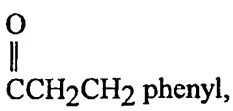
I

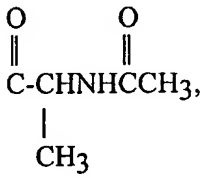
wherein R^1 is

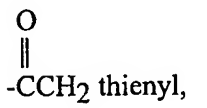


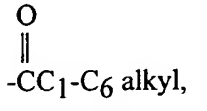












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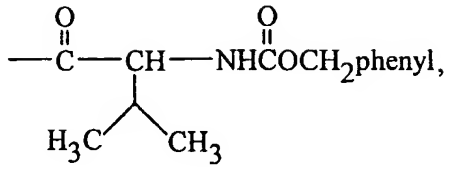
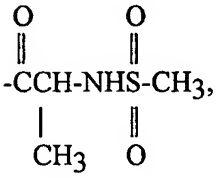
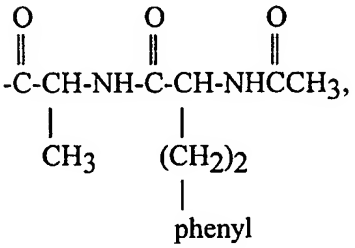
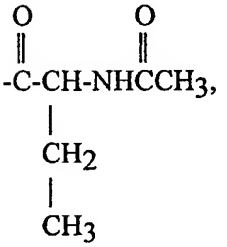
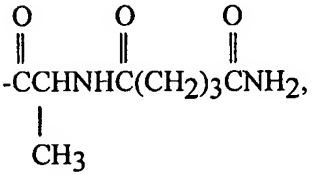
-$(CH_2)_3$ phenyl,

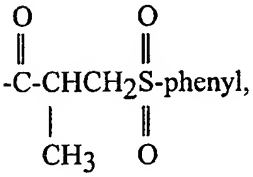


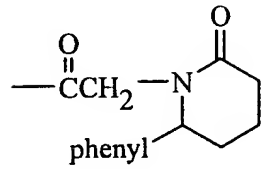


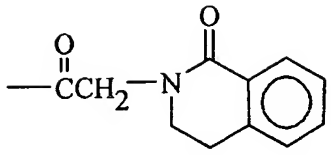


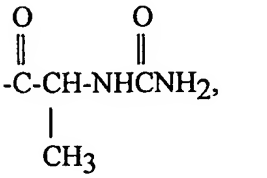


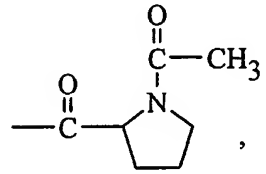


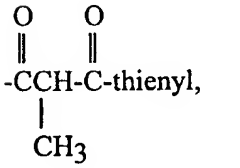


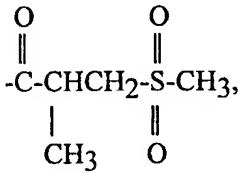


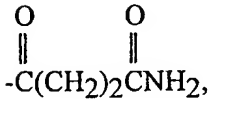


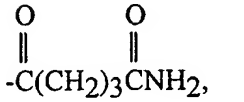


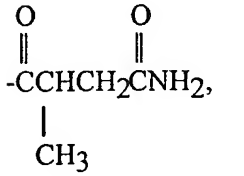


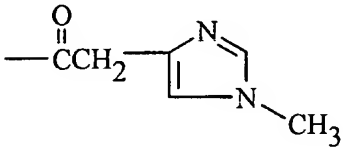


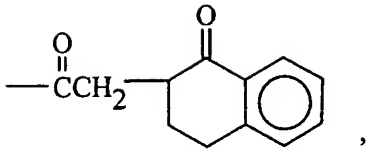








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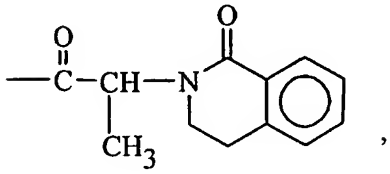
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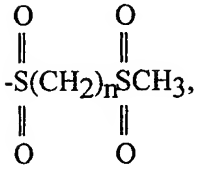
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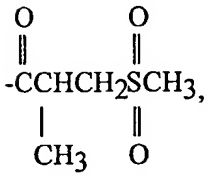
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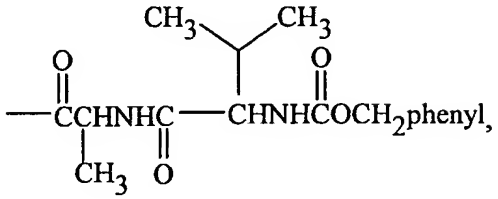
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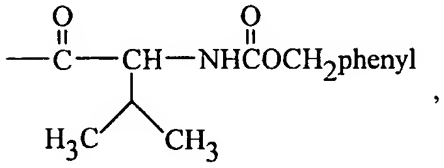
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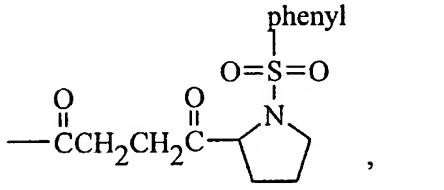
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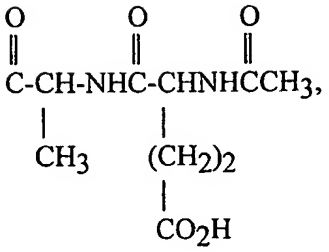

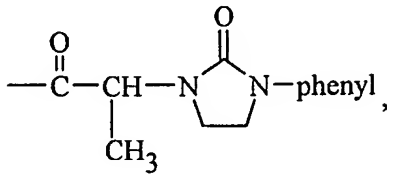

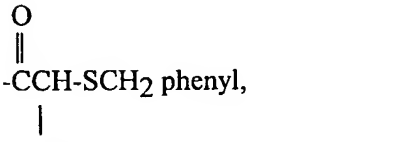

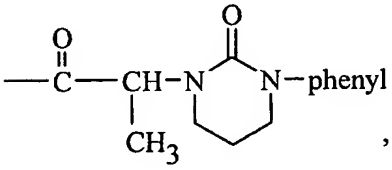

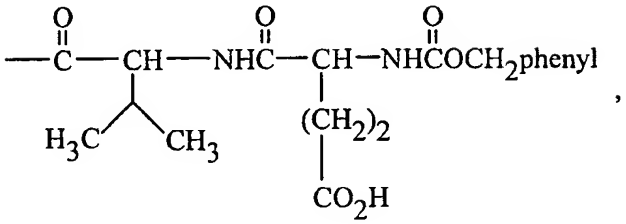

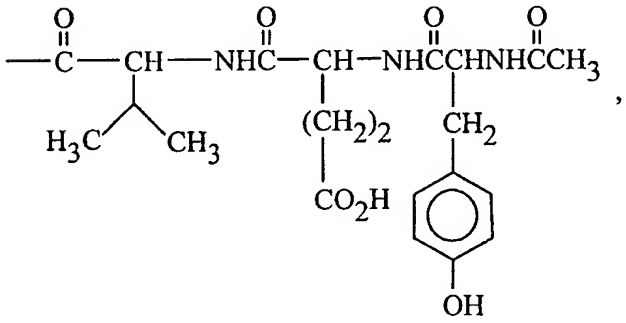

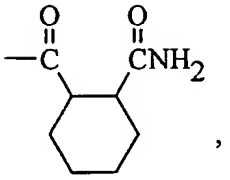

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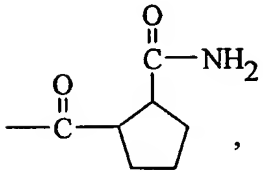

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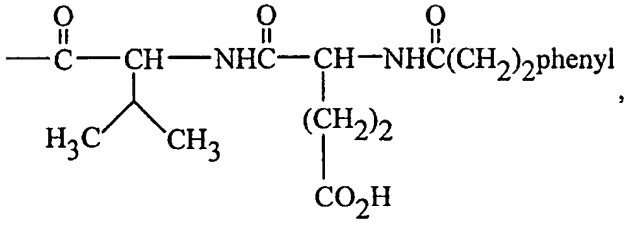

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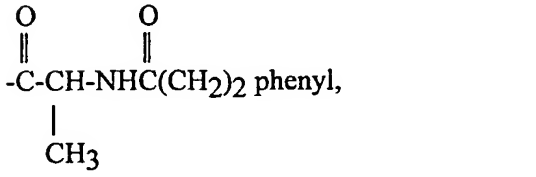

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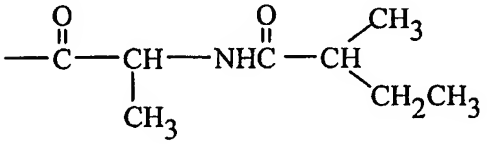

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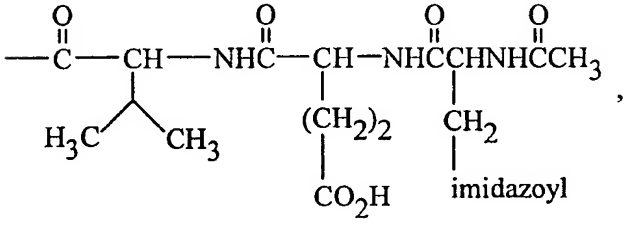

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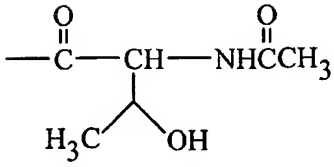

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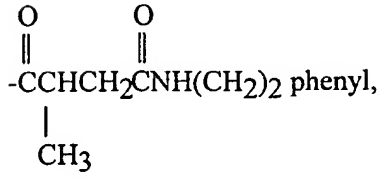

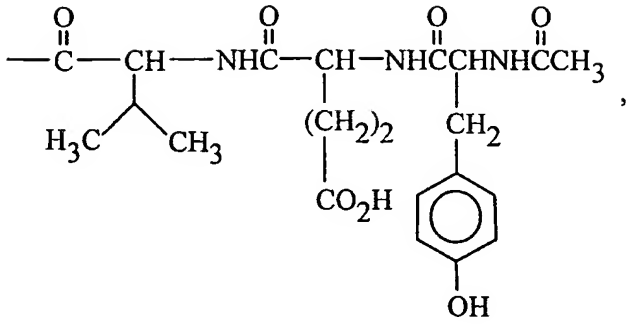

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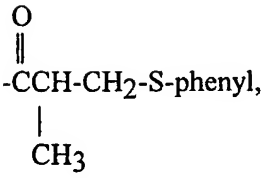

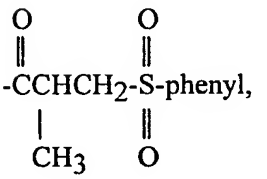

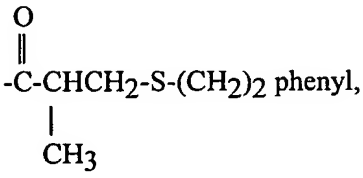

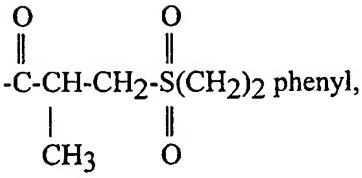

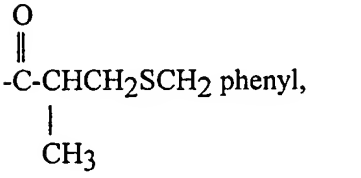

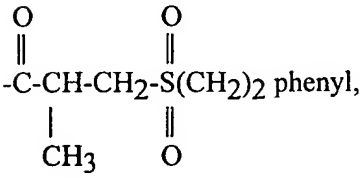

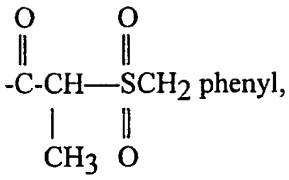

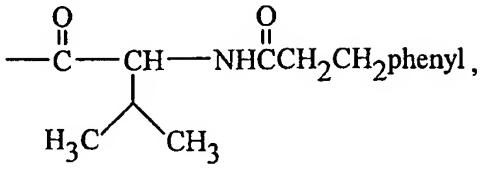

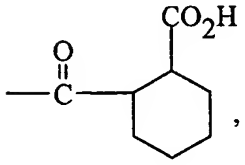

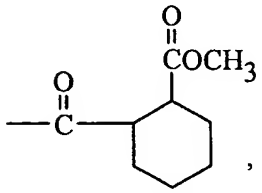

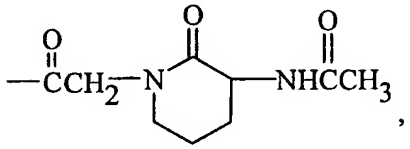

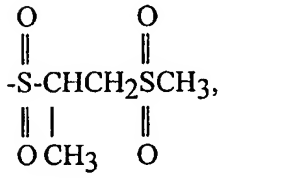

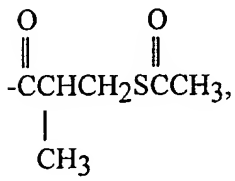

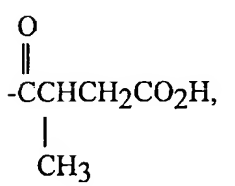

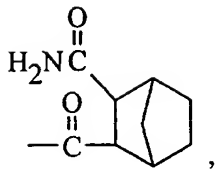

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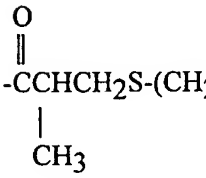
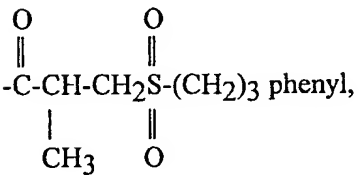
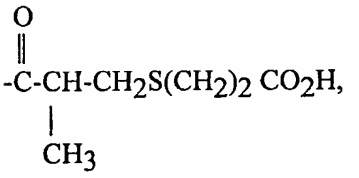
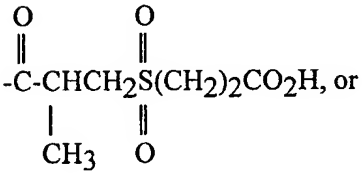
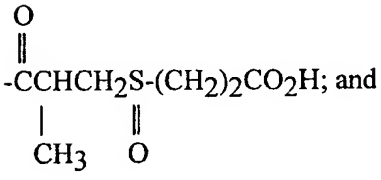










R^2 is

-CH_2CH_2 phenyl,

-CH_2 naphthyl,

-CH_2CH_2 cyclohexyl,

-CH_2O naphthyl,

-CH_2O phenyl,

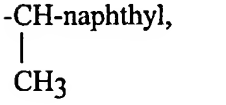
-CH_2S-phenyl,

-CH_2-substituted naphthyl,

$-CH_2CH(phenyl)_2$,

$-CH_2$-imidazole,

$-(CH_2)_3$-phenyl,



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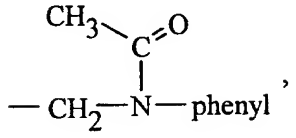

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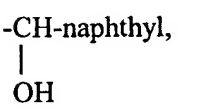
$-CH[CH_2phenyl]_2$,



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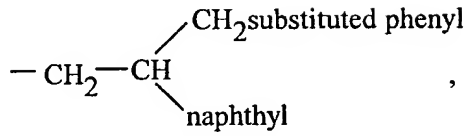

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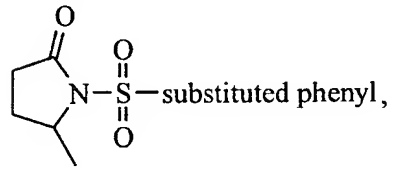
$-CH_2$-naphthyl-phenyl,

$-CH_2$-fluorenyl,

$-CH_2$ naphthyl-thienyl,



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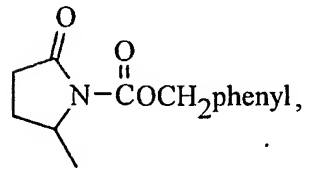

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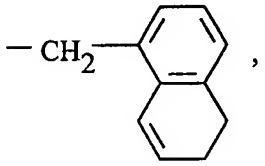
$-CH_2$-benzofuranyl,

-CH_2-benzothienyl,

-CH_2-naphthyl-CH_2 phenyl,

-CH_2-substituted phenyl,



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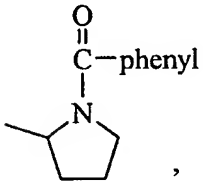
-CH_2-substituted indolyl,



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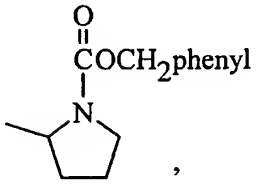

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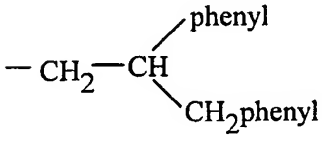

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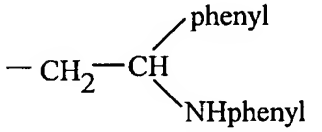

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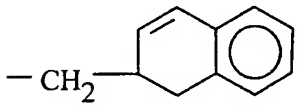

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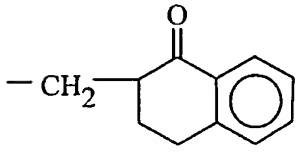

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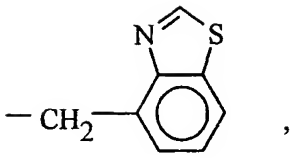

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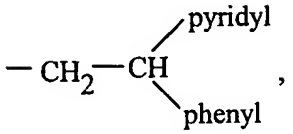

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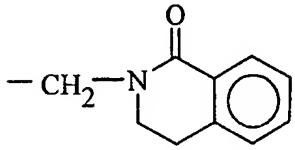
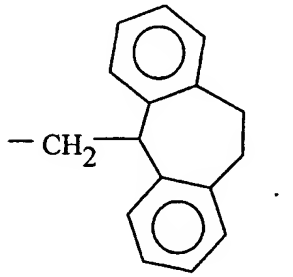


,

-$(CH_2)_2$ pyridyl, or



,

each n is independently 0 to 3, and the pharmaceutically acceptable, salts, esters, amides, and prodrugs thereof.

DETAILED DESCRIPTION OF THE INVENTION

The term "alkyl" means a straight or branched chain hydrocarbon. Representative examples of alkyl groups are methyl, ethyl, propyl, isopropyl, isobutyl, butyl, tert-butyl, sec-butyl, pentyl, and hexyl.

The term "alkoxy" means an alkyl group attached to an oxygen atom. Representative examples of alkoxy groups include methoxy, ethoxy, tert-butoxy, propoxy, and isobutoxy.

The term "halogen" includes chlorine, fluorine, bromine and iodine.

The term "aryl" means an aromatic hydrocarbon. Representative examples of aryl groups include phenyl and naphthyl.

The term "heteroatom" includes oxygen, nitrogen, sulfur, and phosphorus.

The term "heteroaryl" means an aryl group wherein one or more carbon atom of the aromatic hydrocarbon has been replaced with a heteroatom. Examples of heteroaryl groups include furan, thiophene, pyrrole, thiazole, pyridine, pyrimidine, pyrazine, benzofuran, indole, coumarin, quinoline, isoquinoline, and naphthyridine.

The aryl or heteroaryl groups may be substituted with one or more substituents, which can be the same or different. Examples of suitable substituents include alkyl, alkoxy, thioalkoxy, hydroxy, halogen, trifluoromethyl, amino, alkylamino, dialkylamino, $-NO_2$, -CN, $-CO_2H$, $-CO_2$alkyl, $-SO_3H$, -CHO, -COalkyl, $-CONH_2$, -CONH-alkyl, $-CONHR^q$, $-CON(alkyl)_2$, $-(CH_2)_n-NH_2$, $-(CH_2)_nOH$, $-(CH_2)_n$-NH-alkyl, $-NHR^q$, or $-NHCOR^q$, where n is 1 to 5 and R^q is hydrogen or alkyl.

The term "cycloalkyl" means a cyclic alkyl group. Examples of cycloalkyl groups include cyclopropane, cyclobutane, cyclopentane, and cyclohexane.

The term "heterocycle" means a cycloalkyl group on which one or more carbon atom has been replaced with a heteroatom. Examples of heterocycles include piperazine, morpholino, and piperidine.

The terms aryl, heteroaryl, cycloalkyl, and heterocycle as used herein include substituted aryl, substituted heteroaryl, substituted cycloalkyl, and substituted heterocycle.

The symbol "—" means a bond.

The compounds of Formula I can be administered to a patient either alone or as part of a pharmaceutically acceptable composition. The compositions can be administered to patients such as humans and animals either orally, rectally, parenterally (intravenously, intramuscularly, or subcutaneously), intracisternally, intravaginally, intraperitoneally, intravesically, locally (powders, ointments, or drops), or as a buccal or nasal spray.

Compositions suitable for parenteral injection may comprise physiologically acceptable sterile aqueous or nonaqueous solutions, dispersions, suspensions or emulsions, and sterile powders for reconstitution into sterile

injectable solutions or dispersions. Examples of suitable aqueous and nonaqueous carriers, diluents, solvents, or vehicles include water, ethanol, polyols (propyleneglycol, polyethyleneglycol, glycerol, and the like), suitable mixtures thereof, vegetable oils (such as olive oil), and injectable organic esters such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersions and by the use of surfactants.

These compositions may also contain adjuvants such as preserving, wetting, emulsifying, and dispensing agents. Prevention of the action of microorganisms can be ensured by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, and the like. It may also be desirable to include isotonic agents, for example sugars, sodium chloride, and the like. Prolonged absorption of the injectable pharmaceutical form can be brought about by the use of agents delaying absorption, for example, aluminum monostearate and gelatin.

Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is admixed with at least one inert customary excipient (or carrier) such as sodium citrate or dicalcium phosphate or,

(a) fillers or extenders, as for example, starches, lactose, sucrose, glucose, mannitol, and silicic acid;

(b) binders, as for example, carboxymethylcellulose, alignates, gelatin, polyvinylpyrrolidone, sucrose, and acacia;

(c) humectants, as for example, glycerol;

(d) disintegrating agents, as for example, agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain complex silicates, and sodium carbonate;

(e) solution retarders, as for example paraffin;

(f) absorption accelerators, as for example, quaternary ammonium compounds;

(g) wetting agents, as for example, cetyl alcohol, and glycerol monostearate;

(h) adsorbents, as for example, kaolin and bentonite; and

(i) lubricants, as for example, talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, or mixtures thereof. In the case of capsules, tablets, and pills, the dosage forms may also comprise buffering agents.

Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethyleneglycols, and the like.

Solid dosage forms such as tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells, such as enteric coatings and others well known in the art. They may contain opacifying agents, and can also be of such composition that they release the active compound or compounds in a certain part of the intestinal tract in a delayed manner. Examples of embedding compositions which can be used are polymeric substances and waxes. The active compounds can also be in micro-encapsulated form, if appropriate, with one or more of the above-mentioned excipients.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art, such as water or other solvents, solubilizing agents and emulsifiers, as for example, ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propyleneglycol, 1,3-butyleneglycol, dimethylformamide, oils, in particular, cottonseed oil, groundnut oil, corn germ oil, olive oil, castor oil, and sesame oil, glycerol, tetrahydrofurfuryl alcohol, polyethyleneglycols, and fatty acid esters of sorbitan or mixtures of these substances, and the like.

Besides such inert diluents, the composition can also include adjuvants, such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

Suspensions, in addition to the active compounds, may contain suspending agents, as for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol

and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, or mixtures of these substances, and the like.

Compositions for rectal administrations are preferably suppositories which can be prepared by mixing the compounds of the present invention with suitable non-irritating excipients or carriers such as cocoa butter, polyethyleneglycol, or a suppository wax, which are solid at ordinary temperatures but liquid at body temperature and therefore, melt in the rectum or vaginal cavity and release the active component.

Dosage forms for topical administration of a compound of this invention include ointments, powders, sprays, and inhalants. The active component is admixed under sterile conditions with a physiologically acceptable carrier and any preservatives, buffers, or propellants as may be required. Ophthalmic formulations, eye ointments, powders, and solutions are also contemplated as being within the scope of this invention.

The compounds of the present invention can be administered to a patient at dosage levels in the range of about 0.1 to about 1,000 mg per day. For a normal human adult having a body weight of about 70 kg, a dosage in the range of about 0.01 to about 100 mg/kg of body weight per day is preferable. The specific dosage used, however, can vary. For example, the dosage can depend on a numbers of factors including the requirements of the patient, the severity of the condition being treated, and the pharmacological activity of the compound being used. The determination of optimum dosages for a particular patient is well known to those skilled in the art.

The term "pharmaceutically acceptable salts, esters, amides, and prodrugs" as used herein refers to those carboxylate salts, amino acid addition salts, esters, amides, and prodrugs of the compounds of the present invention which are, within the scope of sound medical judgement, suitable for use in contact with the tissues of patients without undue toxicity, irritation, allergic response, and the like, commensurate with a reasonable benefit/risk ratio, and effective for their intended use, as well as the zwitterionic forms, where possible, of the compounds of the invention. The term "salts" refers to the relatively non-toxic, inorganic and organic acid addition salts of compounds of the present invention. These salts can be

prepared in situ during the final isolation and purification of the compounds or by separately reacting the purified compound in its free base form with a suitable organic or inorganic acid and isolating the salt thus formed. Representative salts include the hydrobromide, hydrochloride, sulfate, bisulfate, nitrate, acetate, oxalate, valerate, oleate, palmitate, stearate, laurate, borate, benzoate, lactate, phosphate, tosylate, citrate, maleate, fumarate, succinate, tartrate, naphthylate mesylate, glucoheptonate, lactobionate, and laurylsulphonate salts and the like. These may include cations based on the alkali and alkaline earth metals, such as sodium, lithium, potassium, calcium, magnesium, and the like, as well as nontoxic ammonium, quaternary ammonium, and amine cations including, but not limited to ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, ethylamine and the like. (See, for example, Berge S.M., et al., "Pharmaceutical Salts," J. Pharm. Sci., 1977;66:1-19, which is incorporated herein by reference).

Examples of pharmaceutically acceptable, non-toxic esters of the compounds of this invention include C_1-C_6 alkyl esters wherein the alkyl group is a straight or branched chain. Acceptable esters also include C_5-C_7 cycloalkyl esters as well as arylalkyl esters such as, but not limited to benzyl. C_1-C_4 alkyl esters are preferred. Esters of the compounds of the present invention may be prepared according to conventional methods.

Examples of pharmaceutically acceptable, non-toxic amides of the compounds of this invention include amides derived from ammonia, primary C_1-C_6 alkyl amines and secondary C_1-C_6 dialkyl amines wherein the alkyl groups are straight or branched chain. In the case of secondary amines the amine may also be in the form of a 5- or 6-membered heterocycle containing one nitrogen atom. Amides derived from ammonia, C_1-C_3 alkyl primary amines and C_1-C_2 dialkyl secondary amines are preferred. Amides of the compounds of the invention may be prepared according to conventional methods.

The term "prodrug" refers to compounds that are rapidly transformed in vivo to yield the parent compound of the above formulae, for example, by hydrolysis in blood. A thorough discussion is provided in Higuchi T. and

Stella V., "Pro-drugs as Novel Delivery Systems," Vol. 14 of the A.C.S. Symposium Series, and in *Bioreversible Carriers in Drug Design,* ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987, both of which are incorporated herein by reference.

In addition, the compounds of the present invention can exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like. In general, the solvated forms are considered equivalent to the unsolvated forms for the purposes of the present invention.

The compounds of the present invention can exist in different stereoisomeric forms by virtue of the presence of asymmetric centers in the compounds; ie, each asymmetric carbon can have either the R or S configuration. It is contemplated that all stereoisomeric forms of the compounds as well as mixtures thereof, including racemic mixtures, form part of this invention.

The compounds of the present invention are administered to a patient in need of ICE or Caspase-4 inhibition. In general, patients in need of ICE or Caspase-4 inhibition are those patients having a disease or condition in which ICE or Caspase-4 plays a role. Examples of such diseases include, but are not limited to, inflammatory diseases such as rheumatoid arthritis and inflammatory bowel disease, neuroinflammatory disorders such as stroke, and septic shock. Other diseases include reperfusion injury, Alzheimer's disease, and shigellosis.

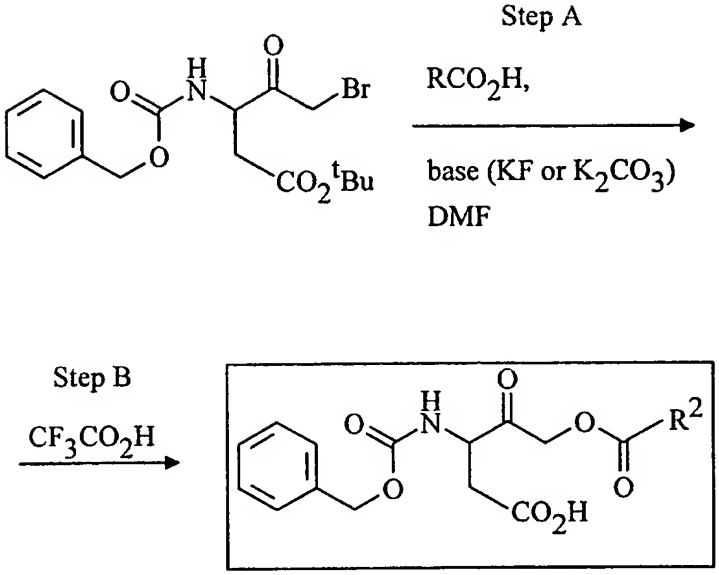
A "therapeutically effective amount" is an amount of a compound of Formula I that when administered to a patient having a disease that can be treated with a compound of Formula I ameliorates a symptom of the disease. A therapeutically effective amount of a compound of Formula I is readily determined by one skilled in the art by administering a compound of Formula I to a patient and observing the results.

The following examples illustrate particular embodiments of the invention and are not intended to limit the scope of the specification and claims in any manner.

EXAMPLES

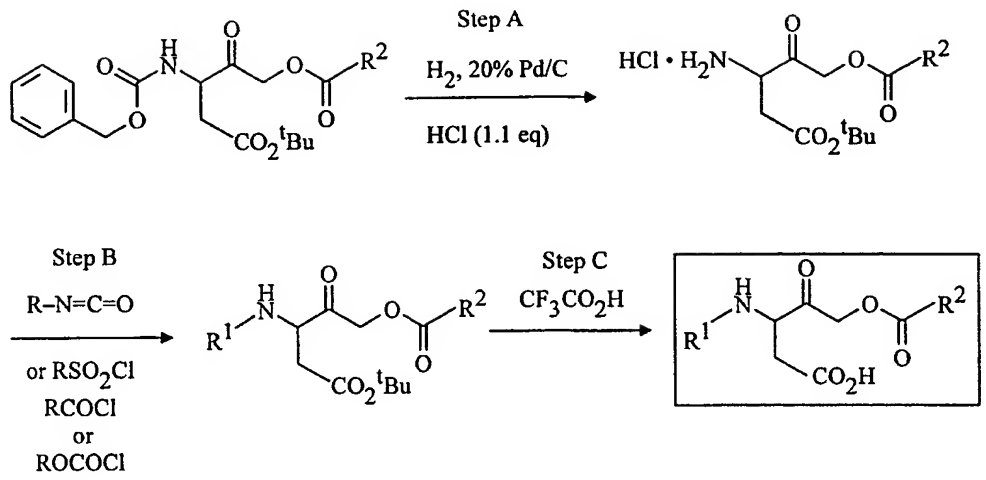
The following Schemes 1 through 11 show generally how compounds of the present invention can be made.

Scheme 1



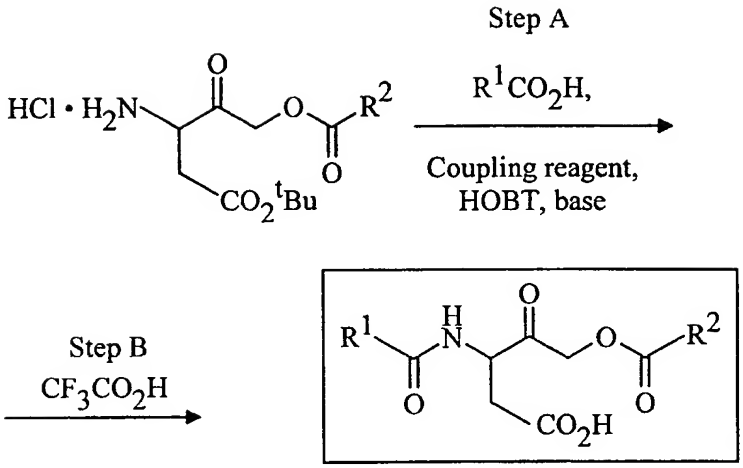
3-Benzyloxycarbonylamino-5-bromo-4-oxo-pentozoic acid tert-butyl ester, also known as Z-Asp(OtBu)-bromomethyl ketone, can be purchased commercially or prepared according to the procedure of Dolle, et al., J. Med. Chem., 1994;37:563-564. This methylbromo ketone is treated with an appropriately substituted carboxylic acid and a base such as potassium fluoride. Alternately, other bases such as potassium carbonate, cesium carbonate, or potassium t-butoxide could be used. The reagents should be mixed in dimethyl formamide (DMF), dimethylacetamide (DMA), dimethyl sulfoxide (DMSO), acetonitrile or other appropriate solvent and stirred at room temperature for 8 to 24 hours. The t-butyl ester protecting group can be removed in acidic media ,preferably trifluoroacetic acid, to produce the carbobenzoxy aspartyl esters shown in Scheme 1.

Scheme 2



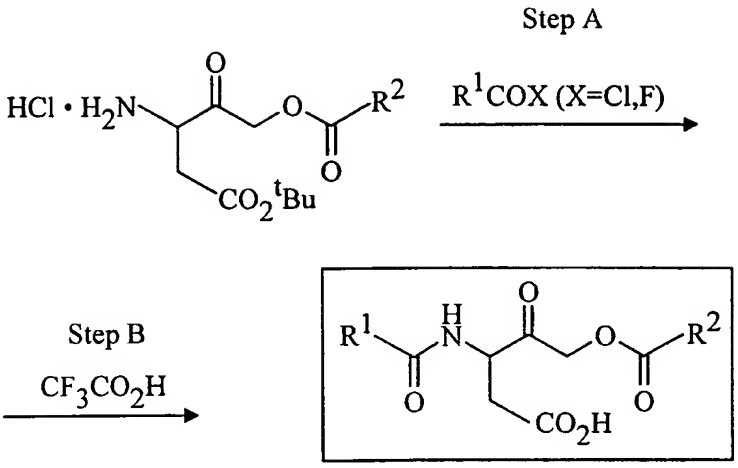
A mixture of an appropriately substituted acyloxymethyl ketone of a carbobenzoxy aspartyl t-butyl ester was hydrogenated with an equivalent of hydrochloric or other acid in the presence of a catalyst such as palladium on carbon to yield the amine salt. The salt can be acylated with an appropriately substituted isocyanate, sulfonyl chloride, chloroformate or phenylpropionyl chloride to afford the N-substituted derivatives. These isocyantes, sulfonyl chlorides, or chloro formates can be purchased commercially or synthesized by methods described in the chemical literature. The t-butyl ester protecting group can be removed in the final step using acidic media, preferably trifluoroacetic acid, to produce the acyloxy methylketone derivatives shown in Scheme 2.

Scheme 3



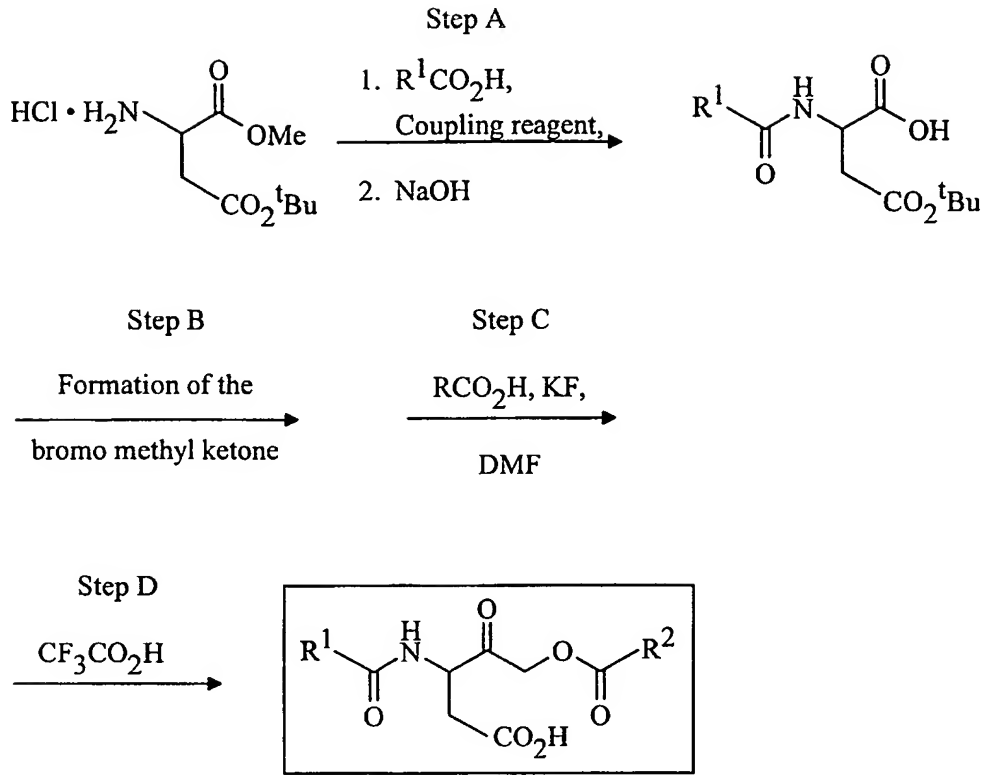
In a manner similar to Example 2, the amine salt of the acyloxymethyl ketone of Z-Asp(Ot-Bu)OH was synthesized and treated with an appropriately substituted carboxylic acid and coupling reagent. The coupling agent may be, but is not limited to, such reagents as 1,3-dicyclohexylcarbodiimide (DCC), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI), 1,1′-carbonyldiimidazole (CDI), 1,1′-carbonylbis(3-methylimidazolium) triflate (CBMIT), isobutylchloroformate, benzotriazol-1-yloxytris(dimethylamino)-phosphonium hexafluorophosphate (BOP), 2-(3,4-dihydro-4-oxo-1,2,3-benzotriazin-3-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TDBTU), and 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU). 1-Hydroxybenzotriazole hydrate should be added to the reaction to improve yield and limit isomerization and base, preferably an amine such as trimethyl amine or methyl morpholine should be added as an acid scavenger. The resulting amide product was treated with acidic media, preferably trifluoroacetic acid, to remove the t-butyl ester and produce the final products as described in Scheme 3.

Scheme 4



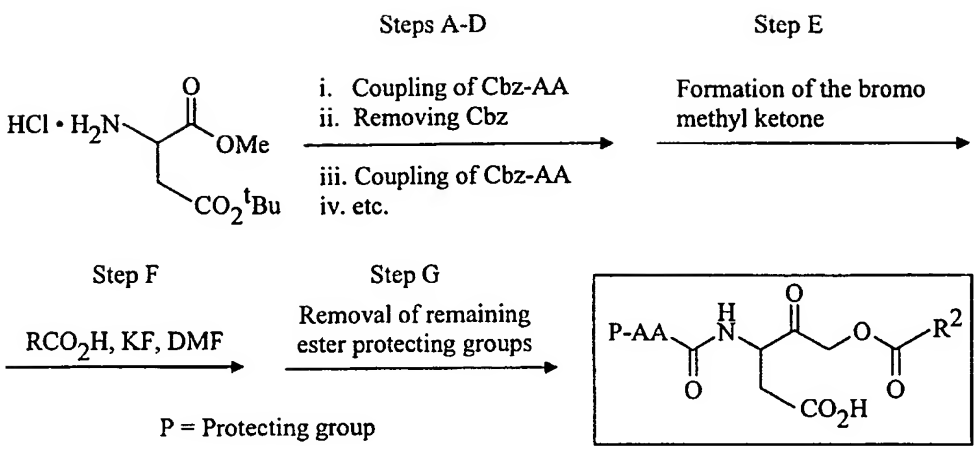
In a manner similar to Example 2, the amine salt of the acyloxymethyl ketone of Cbz-Asp(OtBu)OH was synthesized and treated with an appropriately substituted acid chloride or acid fluoride to generate an amide product. The acid chlorides were purchased commercially or were prepared by treating carboxylic acids with agents such as thionyl chloride, phosphorous tribromide, or oxalyl chloide/DMF. The acid fluorides were prepared by treating a carboxylic acid with cyanuric fluoride. The penultimate amide product was treated with acidic media preferably trifluoroacetic acid to remove the t-butyl ester and afford the final products as described in Scheme 4.

Scheme 5



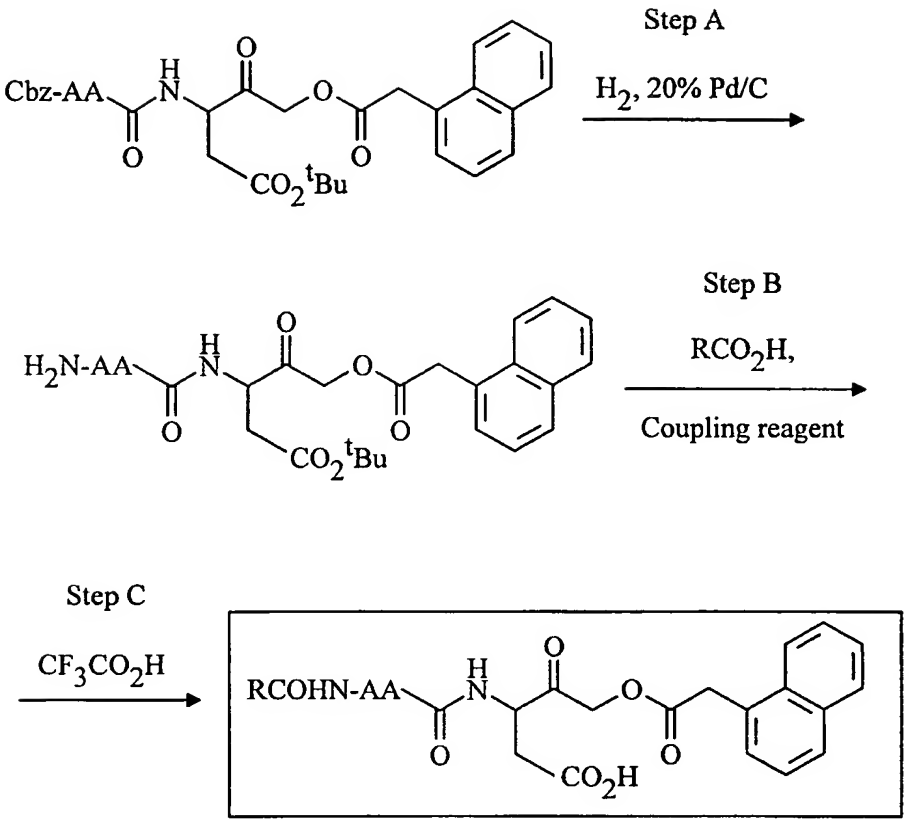
The hydrochloride salt of H-Asp(OtBu)OMe was treated with an appropriately substituted carboxylic acid and coupling reagent. The coupling agent may be but is not limited to such reagents described in Example 3. 1-Hydroxybenzotriazole hydrate should be added to the reaction to improve yield and limit isomerization and base, preferably an amine such as trimethyl amine or methyl morpholine should be added as an acid scavenger. The resulting amide product was treated with an alkaline reagent such as sodium hydroxide to hydrolyze the methyl ester to the carboxylic acid. The resulting acid was treated with a chloroformate such as isobutylchloroformate, followed by diazomethane and then hydrobromic acid to afford the methyl bromo ketone. Treatment of the methylbromo ketone with an appropriately substituted carboxylic acid and a base such as potassium fluoride (as described in Example 1) produced the desired acyloxymethyl ketones which were deprotected as described previously with trifluoroacetic acid to afford the final compounds as described in Scheme 5.

Scheme 6



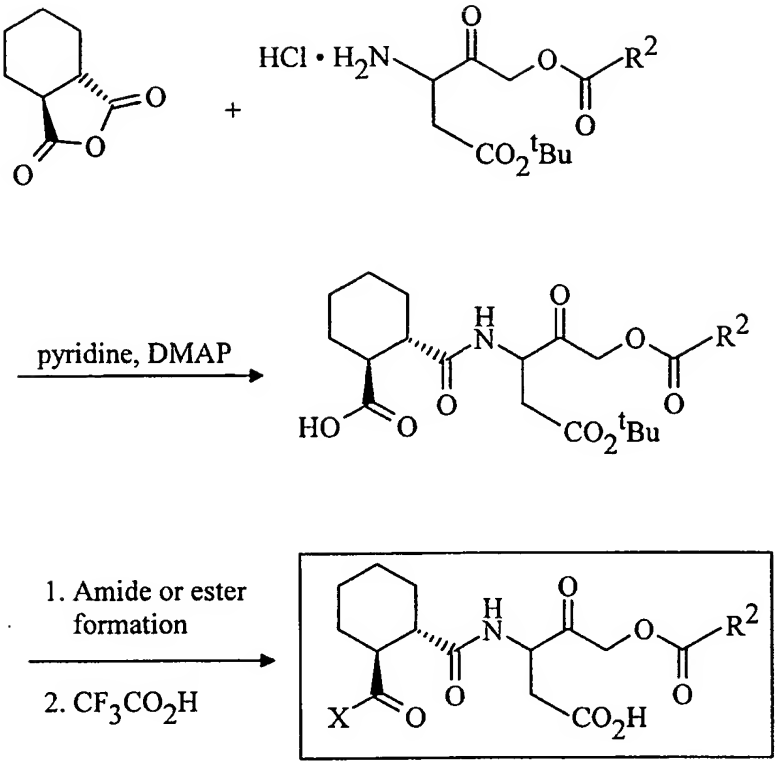
The hydrochloride salt of H-Asp(OtBu)OMe was treated with an appropriately protected amino acid and coupling reagent. The coupling agent may be, but is not limited to, such reagents as described in Example 3. 1-Hydroxybenzotriazole hydrate should be added to the reaction to improve yield and limit isomerization and base, preferably an amine such as trimethyl amine or methyl morpholine should be added as an acid scavenger. The resulting amide product was treated with an alkaline reagent such as sodium hydroxide to hydrolyze the methyl ester to the carboxylic acid. The Cbz-amine protecting group was removed using standard catalytic hydrogenation conditions and coupling of another protected amino acid can proceed as described above. This process was repeated until the peptide was the desired length. The resulting peptide product was treated with an alkaline reagent such as sodium hydroxide to hydrolyze the methyl ester to the carboxylic acid. The resulting acid was subsequently treated with a chloroformate such as isobutylchloroformate, followed by diazomethane and then hydrobromic acid to afford the methylbromo ketone. Treatment of the methylbromo ketone with an appropriately substituted carboxylic acid and a base such as potassium fluoride (as described in Example 1) produced the desired acyloxymethyl ketones which were deprotected as described previously with trifluoroacetic acid to afford the final compounds as described in Scheme 6.

Scheme 7



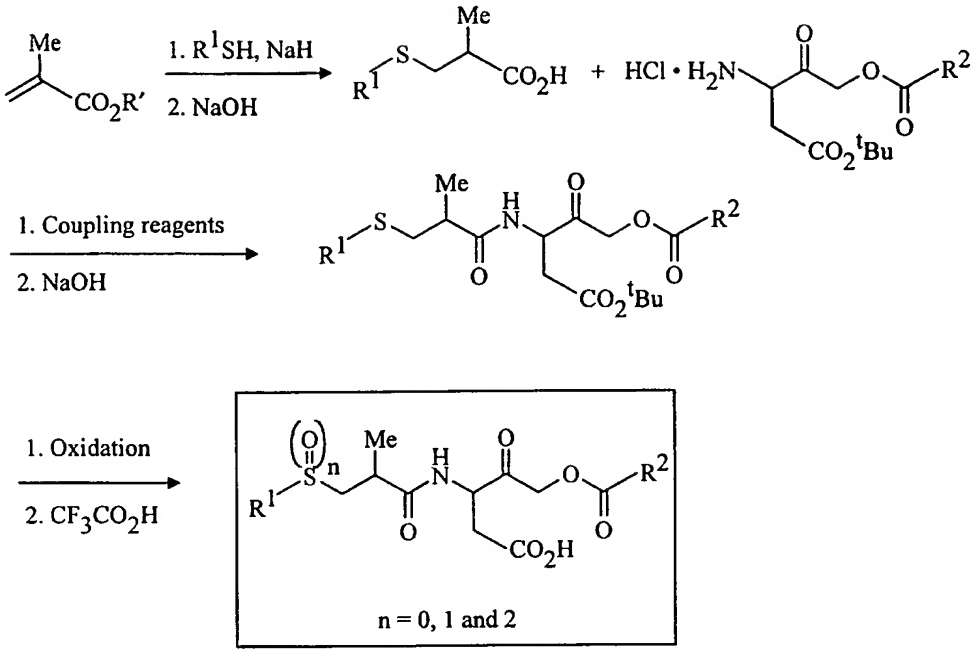
The appropriately substituted acyloxymethyl ketone of a protected amino acid was synthesized as described in Example 7. The Cbz-amine protecting group was removed using standard catalytic hydrogenation conditions, and the amine product was treated with an appropriately substituted carboxylic acid and a coupling reagent. The coupling agent may be, but is not limited to, such reagents described in Example 3. 1-Hydroxybenzotriazole hydrate should be added to the reaction to improve yield and limit isomerization and base, preferably an amine such as trimethyl amine or methyl morpholine should be added as an acid scavenger. The penultimate amide product was treated with acidic media preferably trifluoroacetic acid to remove the t-butyl ester and afford the final products as described in Scheme 7.

Scheme 8



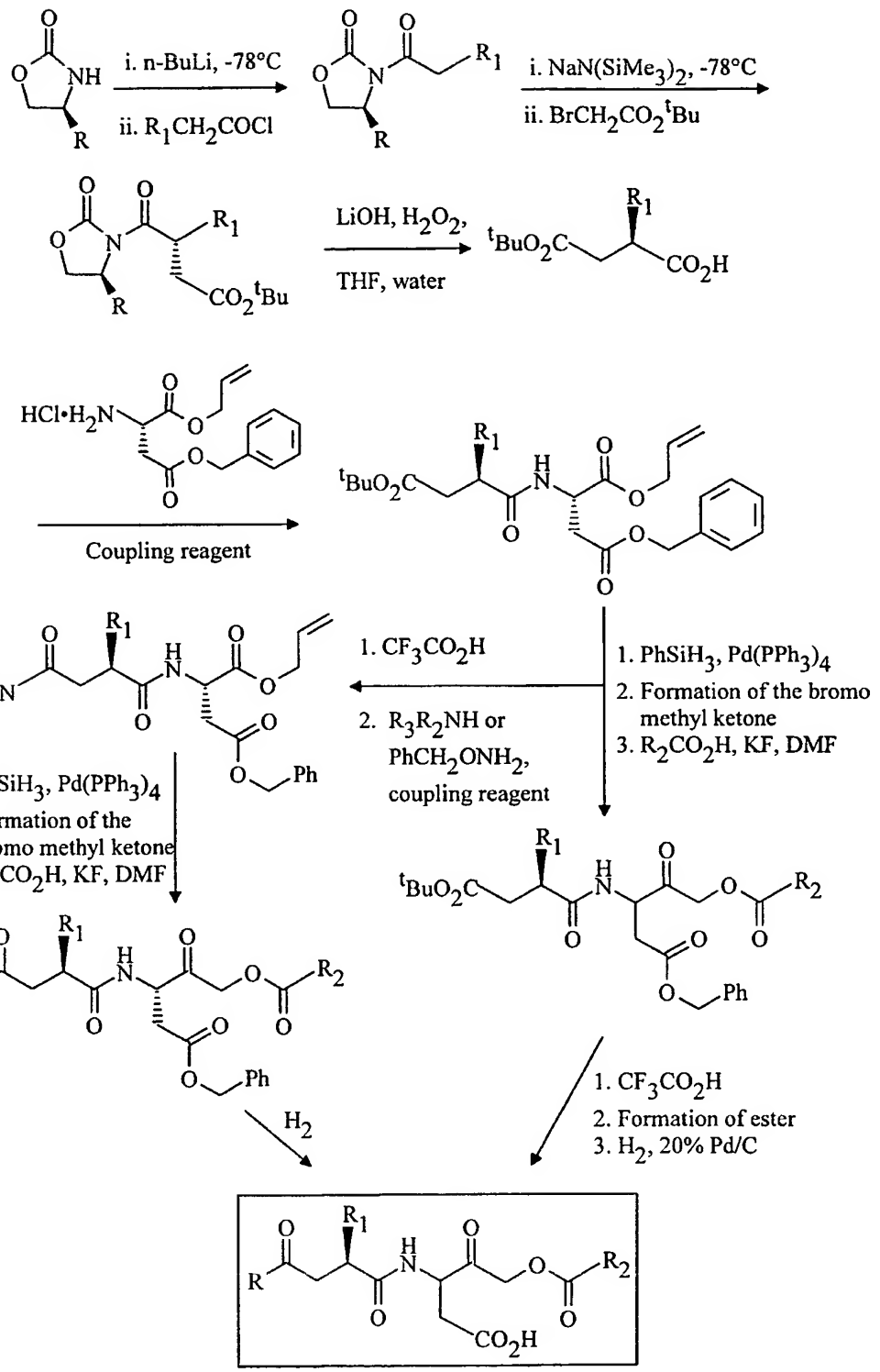
Trans-1,2-cyclohexanedicarboxylic anhydride was treated with the amine salt of an appropriately substituted acyloxymethyl ketone of aspartyl t-butyl ester in the presence of pyridine and 4-dimethylaminopyridine (DMAP) to yield the amide product. The carboxylic acid can be functionalized with appropriately substituted amines or alcohols and standard coupling reagents as described in Example 3 to afford amide and ester products. The penultimate product was treated with acidic media, preferably trifluoroacetic acid, to remove the t-butyl ester and afford the final products as described in Scheme 8.

Scheme 9



Methyl methacrylate was treated with the anion of an appropriately substituted sulfide to afford the Michael adduct which was hydrolyzed in basic media such as sodium hydroxide to produce the carboxylic acid. This acid was combined with the amine salt of the acyloxymethyl ketone of aspartyl t-butyl ester and a coupling reagent such as those described in Example 3 to obtain the amide product. If the sulfide (where n = 0) is the desired product, no oxidation step is employed, and the amide t-butyl ester is deprotected in acidic media, preferably trifluoroacetic acid, to afford the final product. Alternately, if the sulfoxide (n = 1) or sulfone (n = 2) is the final product, the amide intermediate is treated with an oxidizing agent which may be, but is not limited to, m-chloroperbenzoic acid, potassium monoperoxysulfate, or sodium perborate to obtain the desired oxidized product. The t-butyl ester of the penultimate intermediate was deprotected in acidic media, preferably trifluoroacetic acid, to afford the final compounds as described in Scheme 9.

Scheme 10

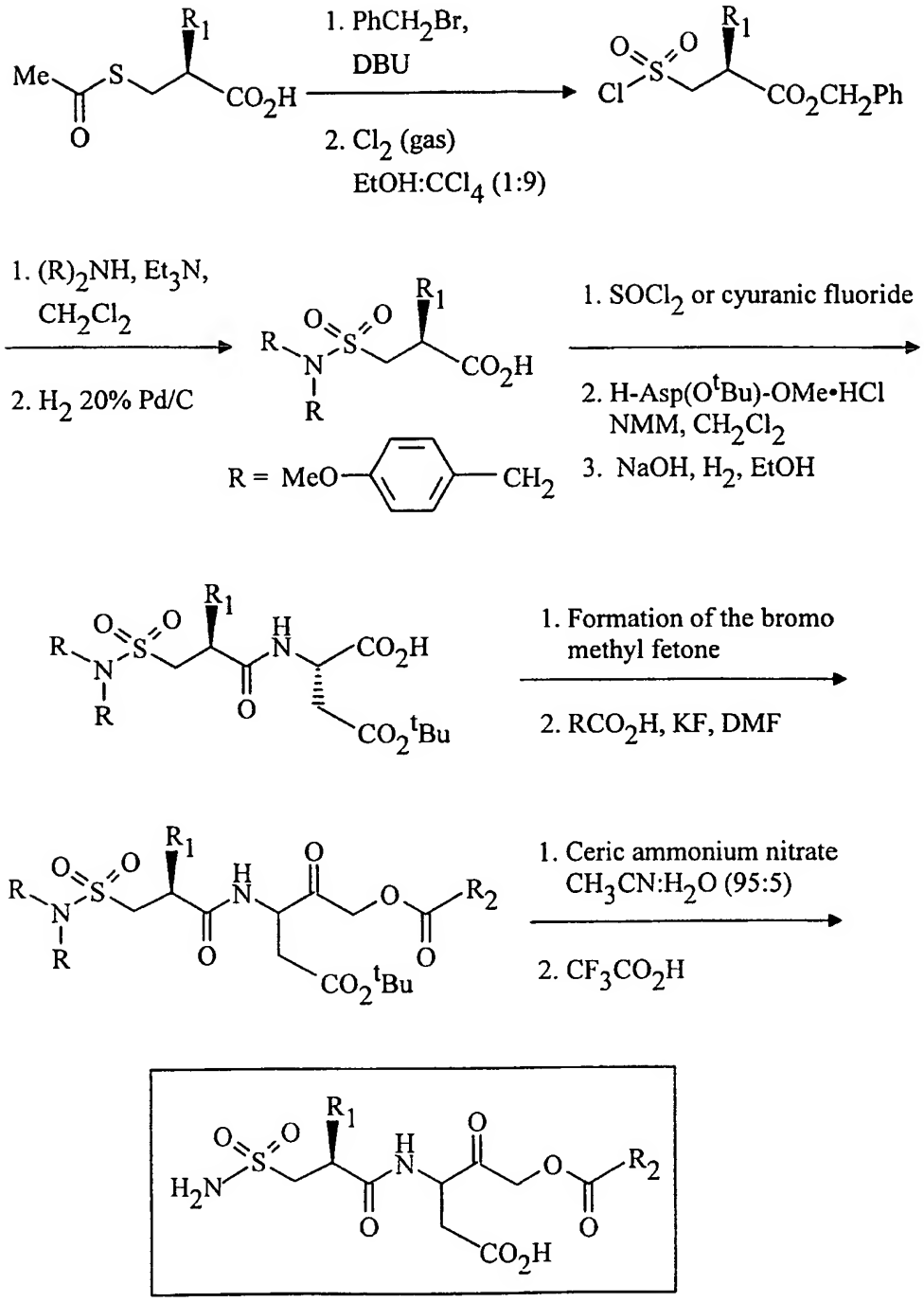

i. n-BuLi, -78°C
ii. R1CH2COCl
i. NaN(SiMe3)2, -78°C
ii. BrCH2CO2tBu
LiOH, H2O2,
THF, water
Coupling reagent
1. CF3CO2H
2. R3R2NH or PhCH2ONH2, coupling reagent
1. PhSiH3, Pd(PPh3)4
2. Formation of the bromo methyl ketone
3. R2CO2H, KF, DMF
1. PhSiH3, Pd(PPh3)4
2. Formation of the bromo methyl ketone
3. R2CO2H, KF, DMF
H2
1. CF3CO2H
2. Formation of ester
3. H2, 20% Pd/C

A 4-substituted-2-oxazolidinone chiral auxiliary as described by Evans, et al., J. Org. Chem., 1985;50:1830 was mixed with a base, such as but not limited to, n-butyl lithium followed by treatment with an appropriately substituted acid chloride or other activated carboxylic acid to afford the N-acylated product. This product was subsequently treated with a base such as, but not limited to, sodium bis(trimethylsilyl)amide and t-butyl bromoacetate to produce the alkylated chiral product. The chiral auxiliary was removed using lithium hydroxide and hydrogen peroxide to obtain the chiral acid. Treatment of the acid with the amine salt of H-Asp(OBz)O-allyl and a coupling reagent as described in Example 3 afforded the succinyl amide product.

At this stage of the process, the product can be elaborated in one of two ways. First the t-butyl ester was removed in acidic media, preferably trifluoroacetic acid, and the resulting acid was coupled with an appropriately substituted amine in the presence of a coupling reagent as described in Example 3 to form a new amide product. The allyl ester was removed with phenylsilane and tetrakis(triphenyl-phosphine)palladium or other Pd(0) catalyst to obtain the carboxylic acid, and the acid was converted to the methylbromo ketone and subsequently to the acyloxymethyl ketone as described in Example 5. The penultimate intermediate was subjected to catalytic hydrogenation to remove the benzyl ester and afford the final amide products as described in Scheme 10.

Alternatively, in a second route to the final products, the allyl ester is removed using phenylsilane and tetrakistetrakis(triphenylphosphine)palladium or other Pd(0) catalyst to obtain the carboxylic acid. This acid is converted to the methylbromo ketone and subsequently to the acyloxymethyl ketone as described in Example 5. Removal of the t-butyl ester of the acyloxymethyl ketone with trifluoroacidic acid and subsequent conversion of the resulting carboxylic acid to the ester resulted in a new ester product. The esterification can be accomplished using a variety of literature techniques which includes but is not limited to treatment of the carboxylic acid with an appropriately substituted alcohol in the presence of a coupling reagent. The penultimate intermediate was subjected to catalytic hydrogenation to remove the benzyl ester and afford the final ester products as described in Scheme 10.

Scheme 11



The appropriately substituted S-acetyl mercapto carboxylic acid was treated with benzyl bromide and 1,8-diazobicyclo[5.4.0]undec-7-ene (DBU) to

produce the benzyl ester which was subsequently reacted with chlorine gas to yield the sulfonyl chloride. The sulfonyl chloride was treated with N,N-bis(p-methoxybenzyl)amine to afford the sulfonamide which was subjected to catalytic hydrogenation to obtain the intermediate carboxylic acid. The acid was activated using cyuranic fluoride which was then mixed with the amine salt of H-Asp(Ot-Bu)OMe to produce the amide product. The methyl ester was hydrolyzed with sodium hydroxide, and the carboxylic acid was elaborated to the acyloxymethyl ketone by chemistry previously described for Example 5. The p-methyoxybenzyl protecting groups of the sulfonamide were removed using oxidizing conditions preferably, but not limited to ceric ammonium nitrate, and the t-butyl ester protecting group was removed in acidic media preferably with trifluoroacetic acid to afford the desired sulfonamide products as described in Scheme 11.

EXAMPLE 1

3-Benzyloxycarbonylamino-5-(naphthalene-1-yl-acetoxy)-4-oxo-pentanoic acid

Step A

A mixture of Z-Asp(OtBu)-bromomethylketone (Z is carbobenzoxy, also known as cbz, Asp is aspartic acid and tBu is tert-butyl) (2.03 g, 5.07 mmol, purchased from BACHEM Bioscience Inc. or prepared according to the procedure of Dolle R.E., et al., [J. Med. Chem., 1994;37:563-564]), 1-naphthylacetic acid (1.00 g, 5.37 mmol) and potassium fluoride (0.74 g, 12.74 mmol) in 10 mL of dimethylformamide (DMF) was stirred at room temperature for 12 hours. The mixture was partitioned between ethyl acetate and saturated $NaHCO_3$ solution. The ethyl acetate extract was washed with saturated KH_2PO_4 and brine solutions, dried ($MgSO_4$), filtered, and concentrated. Medium pressure chromatography (silica gel, 75% hexanes-25% ethyl acetate) of the crude oil afforded 3-benzyloxycarbonylamino-5-(naphthalene-1-yl-acetoxy)-4-oxo-pentanoic acid tert-butyl ester as a colorless oil.

Step B

A solution of 3-benzyloxycarbonylamino-5-(naphthalene-1-yl-acetoxy)-4-oxo-pentanoic acid tert-butyl ester (0.500 g, 0.989 mmol, Example 1, Step A) and trifluoroacetic acid (10 mL, 0.13 mol) in 20 mL of dichloromethane was stirred at room temperature for 2 hours. The solution was concentrated to give the title compound as a foamy white solid.

Analysis calculated for $C_{25}H_{23}NO_7 \cdot 0.70H_2O$ (462.075):

C, 64.98; H, 5.32; N, 3.03.

Found: C, 64.94; H, 5.01; N, 3.01.

In a process analogous to Example 1, the corresponding compounds were prepared:

EXAMPLE 1a

3-Benzyloxycarbonylamino-4-oxo-5-(3-phenyl-propionyloxy)-pentanoic acid, as white solid.

Analysis calculated for $C_{22}H_{23}NO_7 \cdot 0.25H_2O$ (417.935):

C, 63.23; H, 5.67, N, 3.35.

Found: C, 63.19; H, 5.55; N, 3.27.

EXAMPLE 1b

3-Benzyloxycarbonylamino-5-(3-cyclohexyl-propionyloxy)-4-oxo-pentanoic acid, as white foamy solid.

Analysis calculated for $C_{22}H_{29}NO_7 \cdot 0.67H_2O$ (431.489):

C, 61.24; H, 7.09; N, 3.25.

Found: C, 61.25; H, 6.85; N, 3.21.

EXAMPLE 1c

3-Benzyloxycarbonylamino-5-[(naphthalene-1-yl-oxy)-acetoxy]-4-oxo-pentanoic acid, as white foamy solid.

Analysis calculated for $C_{25}H_{23}NO_8 \cdot 0.40H_2O$ (472.670):

C, 63.53; H, 5.08; N, 2.96.

Found: C, 63.55; H, 4.87; N, 2.77.

EXAMPLE 1d

3-Benzyloxycarbonylamino-4-oxo-5-phenoxyacetoxy-pentanoic acid, as foamy white solid.

Analysis calculated for $C_{21}H_{21}NO_8 \cdot 0.67H_2O$ (427.414):

C, 59.01; H, 5.27; N, 3.28.

Found: C, 58.99; H, 4.91; N. 3.15.

EXAMPLE 1e

3-Benzyloxycarbonylamino-4-oxo-5-phenylsulfanylacetoxy-pentanoic acid, as white solid.

Analysis calculated for $C_{21}H_{21}NO_7S$ (431.468):

C, 58.46; H, 4.91; N, 3.25.

Found: C, 58.08; H, 4.83; N, 3.14.

EXAMPLE 1f

3-Benzyloxycarbonylamino-5-[(6-methoxy-naphthalene-1-yl)-acetoxy]-4-oxo-pentanoic acid, as off-white solid.

Analysis calculated for $C_{26}H_{25}NO_8 \cdot H_2O$ (497.506):

C, 62.77; H, 5.47; N, 2.82.

Found: C, 62.73; H, 5.24; N, 2.61.

EXAMPLE 1g

3-Benzyloxycarbonylamino-5-(naphthalene-2-yl-acetoxy)-4-oxo-pentanoic acid, as off-white solid.

Analysis calculated for $C_{25}H_{23}NO_7 \cdot 0.80H_2O$ (463.877):

C, 64.73; H, 5.34; N, 3.02.

Found: C, 64.64; H, 4.94; N, 2.88.

EXAMPLE 1h

3-Benzyloxycarbonylamino-5-(3-naphthalene-2-yl-propionyloxy)-4-oxo-pentanoic acid, as white solid.

Analysis calculated for $C_{26}H_{25}NO_7$ (463.492):

C, 67.38; H, 5.44; N, 3.02.

Found: C, 64.39; H, 5.10; N, 2.76.

EXAMPLE 1i

3-Benzyloxycarbonylamino-5-(3,3-diphenyl-propionyloxy)-4-oxo-pentanoic acid, as foamy tan solid.

Analysis calculated for $C_{28}H_{27}NO_7$ (489.530):

C, 68.70; H, 5.56; N, 2.86.

Found: C, 66.68; H, 5.72; N, 3.07.

EXAMPLE 1j

3-Benzyloxycarbonylamino-5-[(1H-indol-3-yl)-acetoxy]-4-oxo-pentanoic acid, as off-white solid.

Analysis calculated for $C_{23}H_{22}N_2O_7 \cdot 0.90H_2O$ (454.655):

C, 60.76; H, 5.28; N, 6.16.

Found: C, 60.76; H, 4.88; N, 5.65.

EXAMPLE 1k

3-Benzyloxycarbonylamino-5-(indol-1-yl-acetoxy)-4-oxo-pentanoic acid, as light purple solid.

Analysis calculated for $C_{23}H_{22}N_2O_7 \cdot 0.75H_2O$ (451.952):

C, 61.12; H, 5.24; N, 6.20.

Found: C, 61.20; H, 5.11; N, 5.90.

EXAMPLE 1l

3-Benzyloxycarbonylamino-5-(2-naphthalene-1-yl-propionyloxy)-4-oxo-pentanoic acid, as white solid.

Analysis calculated for $C_{26}H_{25}NO_7 \cdot 0.20H_2O$ (467.095):

C, 66.86; H, 5.48; N, 3.00.

Found: C, 66.87; H, 5.61; N, 2.71.

EXAMPLE 1m

3-Benzyloxycarbonylamino-4-oxo-5-[(2-oxo-pyrrolidin-1-yl)-acetoxy]-pentanoic acid, as white solid.

Analysis calculated for $C_{19}H_{22}N_2O_8 \cdot 0.50H_2O$ (415.403):

C, 54.94; H, 5.58; N, 6.74.

Found: C, 55.18; H, 5.72; N, 6.36.

EXAMPLE 1n

5-[(Acetyl-phenyl-amino)-acetoxy]-3-benzyloxycarbonyl-amino-4-oxo-pentanoic acid, as off-white solid.

Analysis calculated for $C_{23}H_{24}N_2O_8 \cdot 0.70NaHCO_3$(515.264):

C, 55.25; H, 4.83; N, 5.44.

Found: C, 55.03; H, 4.86; N, 5.41.

EXAMPLE 1o

3-Benzyloxycarbonylamino-5-(2-benzyl-3-phenyl-propionyloxy)-4-oxo-pentanoic acid, potassium salt as hygroscopic white solid.

Analysis calculated for $C_{29}H_{28}NO_7 \cdot K \cdot 0.90H_2O$ (557.865):

C, 62.44; H, 5.38; N, 2.51.

Found: C, 62.40; H, 5.19; N, 2.17.

EXAMPLE 1p

3-Benzyloxycarbonylamino-5-(hydroxy-naphthalene-1-yl-acetoxy)-4-oxo-pentanoic acid, as white solid.

Analysis calculated for $C_{25}H_{23}NO_8 \cdot 0.30H_2O$ (470.869):

C, 63.77; H, 5.05; N, 2.98.

Found: C, 63.73; H, 4.87; N, 2.93.

EXAMPLE 1q

3-Benzyloxycarbonylamino-4-oxo-5-[(phenyl-amino)-acetoxy]-pentanoic acid, trifluoroacetic acid salt, as brown solid.

Analysis calculated for $C_{21}H_{22}N_2O_7 \cdot 0.50CF_3CO_2H$ (471.431):

C, 56.05; H, 4.81; N, 5.94.

Found: C, 55.72; H, 4.98; N, 5.78.

EXAMPLE 1r

3-Benzyloxycarbonylamino-5-[(6-hydroxy-naphthalene-1-yl)-acetoxy]-4-oxo-pentanoic acid, as white solid.

Analysis calculated for $C_{25}H_{23}NO_8 \cdot 0.40H_2O$ (472.670):

C, 63.53; H, 5.08; N, 2.96.

Found: C, 63.53; H, 5.25; N, 2.83.

EXAMPLE 1s

3-Benzyloxycarbonylamino-5-[3-(4-hydroxy-phenyl)-2-naphthalene-1-yl-propionyloxy)-4-oxo-pentanoic acid, as white solid.

Analysis calculated for $C_{32}H_{29}NO_8 \cdot 0.50H_2O$ (564.598):

C, 68.08; H, 5.36; N, 2.48.

Found: C, 67.98; H, 5.40; N, 2.34.

EXAMPLE 1t

(S)-3-Benzyloxycarbonylamino-4-oxo-5-phenylacetoxy-pentanoic acid

^1H NMR (400 MHz, d_6DMSO) 7.31 (m, 10H), 5.05 (s, 2H), 4.92 (m, 2H), 4.45 (m, 1H), 3.75 (s, 2H), 2.71 (dd, 1H), 2.52 (dd, 1H)

EXAMPLE 1u

(S)-3-Benzyloxycarbonylamino-4-oxo-5-(4-phenyl-butyryloxy)-pentanoic acid

^1H NMR (400 MHz, d_6DMSO) 7.86 (bs, 1H), 7.27 (m, 10H), 5.05 (s, 2H), 4.91 (m, 2H), 4.46 (m, 1H), 2.72 (dd, 1H), 2.61 (t, 2H), 2.52 (dd, 1H), 2.36 (t, 2H), 1.83 (m, 2H)

EXAMPLE 1v

3-Benzyloxycarbonylamino-4-oxo-5-[(4-phenyl-naphthalen-1-yl)-acetoxy]-pentanoic acid, as a white solid, mp 111-119°C, dec.

Analysis calculated for $C_{31}H_{27}NO_7$ (525.563):

C, 70.85; H, 5.18; N, 2.67.

Found: C, 70.60; H, 5.11; N, 2.64.

EXAMPLE 1w

3-Benzyloxycarbonylamino-5-[(4-methyl-naphthalen-1-yl)-acetoxy]-4-oxo-pentanoic acid, as a white solid, mp 94-100°C, dec.

Analysis calculated for $C_{26}H_{25}NO_7 \cdot 0.15\ H_2O$ (466.194):

C, 66.99; H, 5.47; N, 3.00.

Found: C, 66.95; H, 5.32; N, 2.94.

EXAMPLE 1x

3-Benzyloxycarbonylamino-4-oxo-5-[(4-thiophen-2-yl-naphthalen-1-yl)-acetoxy]-pentanoic acid, as an off-white solid, mp 63-68°C, dec.

Analysis calculated for $C_{29}H_{25}NO_7S$ (531.589):

C, 65.52; H, 4.74; N, 2.63.

Found: C, 65.32; H, 5.08; N, 2.47.

EXAMPLE 1y

3-Benzyloxycarbonylamino-5-[(4-fluoro-naphthalen-1-yl)-acetoxy]-4-oxo-pentanoic acid, as a white solid, mp 100-103°C, dec.

Analysis calculated for $C_{25}H_{22}FNO_7$ (467.455):

C, 64.24; H, 4.74; N, 3.00.

Found: C, 63.98; H, 4.52; N, 2.89.

EXAMPLE 1z

3-Benzyloxycarbonylamino-5-[(2-methyl-naphthalen-1-yl)-acetoxy]-4-oxo-pentanoic acid, as a white solid, mp 139-144°C.

Analysis calculated for $C_{26}H_{25}NO_7$ (463.492):

C, 67.38; H, 5.44; N, 3.02.

Found: C, 67.09; H, 5.44; N, 2.84.

EXAMPLE 1aa

3-Benzyloxycarbonylamino-5-[(2-fluoro-naphthalen-1-yl)-acetoxy]-4-oxo-pentanoic acid, as a white solid, mp 98-102°C.

Analysis calculated for $C_{25}H_{22}FNO_7$ (467.455):

C, 64.24; H, 4.74; N, 3.00.

Found: C, 63.57; H, 4.47; N, 2.85.

EXAMPLE 1bb

5-(Benzofuran-4-yl-acetoxy)-3-benzyloxycarbonylamino-4-oxo-pentanoic acid, as light yellow oil.

Analysis calculated for $C_{23}H_{21}NO_8 \cdot 0.65\ H_2O$ (451.136):

C, 61.24; H, 4.98; N, 3.10.

Found: C, 61.22; H, 4.80; N, 2.98.

EXAMPLE 1cc

5-(Benzo[b]thiophen-7-yl-acetoxy)-3-benzyloxycarbonylamino-4-oxo-pentanoic acid, as light yellow oil.

Analysis calculated for $C_{23}H_{21}NO_7S \cdot 1.5\ H_2O$ (482.513):

C, 57.25; H, 5.01; N, 2.90.

Found: C, 57.35; H, 4.82; N, 2.76.

EXAMPLE 1dd

5-(Benzo[b]thiophen-4-yl-acetoxy)-3-benzyloxycarbonylamino-4-oxo-pentanoic acid, as a foamy off-white solid.

Analysis calculated for $C_{23}H_{21}NO_7S$ (455.490):

C, 60.65; H, 4.65; N, 3.08.

Found: C, 60.90; H, 4.90; N, 2.92.

EXAMPLE 1ee

5-[(4-Benzyl-naphthalen-1-yl)-acetoxy]-3-benzyloxycarbonylamino-4-oxo-pentanoic acid, as a white solid, mp 66-77°C, dec.

Analysis calculated for $C_{32}H_{29}NO_7 \cdot 0.30\ H_2O$ (544.995):

C, 70.52; H, 5.48; N, 2.57.

Found: C, 70.55; H, 5.35; N, 2.49.

EXAMPLE 1ff

3-Benzyloxycarbonylamino-5-[(3,4-dihydro-naphthalen-1-yl)-acetoxy]-4-oxo-pentanoic acid, as a foamy light yellow solid.

Analysis calculated for $C_{25}H_{25}NO_7 \cdot 0.20\ H_2O$ (455.084):

C, 65.98; H, 5.63; N, 3.08.

Found: C, 66.06; H, 5.74; N, 3.04.

EXAMPLE 1gg

3-Benzyloxycarbonylamino-5-[(5-bromo-1H-indol-3-yl)-acetoxy]-4-oxo-pentanoic acid, as a tan solid, mp 122-129°C, dec.

Analysis calculated for $C_{23}H_{21}BrN_2O_7$ (517.342):

C, 53.40; H, 4.09; N, 5.41.

Found: C, 53.77; H, 3.94; N, 5.25.

EXAMPLE 1hh

3-Benzyloxycarbonylamino-5-(3,4-diphenyl-butyryloxy)-4-oxo-pentanoic acid, as a hygroscopic white solid.

Analysis calculated for $C_{29}H_{29}NO_7 \cdot 0.30\ H_2O$ (508.962):

C, 68.44; H, 5.86; N, 2.75.

Found: C, 68.41; H, 5.92; N, 2.56.

EXAMPLE 1ii

3-Benzyloxycarbonylamino-4-oxo-5-(3-phenyl-3-phenylamino-propionyloxy)-pentanoic acid as a hygroscopic light green solid.

Analysis calculated for $C_{28}H_{28}N_2O_7 \cdot 0.50\ H_2O$ (513.552):

C, 65.49; H, 5.69; N, 5.46.

Found: C, 65.58; H, 5.62; N, 5.19.

EXAMPLE 1jj

3-Benzyloxycarbonylamino-4-oxo-5-[(1,2,3,4-tetrahydro-naphthalen-2-yl)-acetoxy]-pentanoic acid, as a white solid, mp 75-83°C, dec.

Analysis calculated for $C_{25}H_{27}NO_7$ (453.496):

C, 66.21; H, 6.00; N, 3.09.

Found: C, 66.02; H, 5.89; N, 2.96.

EXAMPLE 1kk

3-Benzyloxycarbonylamino-5-[(1-methanesulfonyl-piperidin-4-yl)-acetoxy]-4-oxo-pentanoic acid as a yellow amorphous solid.

Analysis calculated for $C_{21}H_{28}N_2O_9S \cdot 0.25$ EtOAc (506.556):

C, 52.16; H, 5.97; N, 5.53.

Found: C, 51.96; H, 6.09; N, 5.22.

EXAMPLE 1ll

3-Benzyloxycarbonylamino-4-oxo-5-[(2,3,5,6-tetramethyl-phenyl)-acetoxy]-pentanoic acid, mp 139-145°C.

Analysis calculated for $C_{25}H_{29}NO_7$:

C, 65.92; H, 6.42; N, 3.07.

Found: C, 65.66; H, 6.30; N, 2.97.

EXAMPLE 1mm

5-(Benzothiazol-4-yl-acetoxy)-3-benzyloxycarbonylamino-4-oxo-pentanoic acid, as a white solid.

Analysis calculated for $C_{22}H_{20}N_2O_7S \cdot 0.15\ CF_3CO_2H$ (473.582):

C, 56.56; H, 4.29; N, 5.92.

Found: C, 56.52; H, 4.09; N, 6.02.

EXAMPLE 1nn

5-(Benzofuran-3-yl-acetoxy)-3-benzyloxycarbonylamino-4-oxo-pentanoic acid as a foamy white solid.

Analysis calculated for $C_{23}H_{21}NO_8 \cdot 0.14\ CF_3CO_2H$ (455.389):

C, 61.40; H, 4.68; N, 3.08.

Found: C, 61.49; H, 4.86; N, 3.13.

EXAMPLE 1oo

5-(Benzo[b]thiophen-3-yl-acetoxy)-3-benzyloxycarbonylamino-4-oxo-pentanoic acid, mp 110-111°C.

Analysis calculated for $C_{23}H_{21}NO_7S$:

C, 60.65; H, 4.65; N, 3.08; S, 7.04.

Found: C, 60.45; H, 4.67; N, 3.02; S, 7.07.

EXAMPLE 1pp

3-Benzyloxycarbonylamino-4-oxo-5-(3-phenyl-3-pyridin-2-yl-propionyloxy)-pentanoic acid, as an amorphous white solid.

Analysis calculated for $C_{27}H_{26}N_2O_7 \cdot CF_3CO_2H$ (604.542):

C, 57.62; H, 4.50; N, 4.63.

Found: C, 57.32; H, 4.65; N, 4.46.

EXAMPLE 1qq

3-Benzyloxycarbonylamino-5-[(2,3-dichloro-phenyl)-acetoxy]-4-oxo-pentanoic acid, as a white solid.

Analysis calculated for $C_{21}H_{19}Cl_2NO_7 \cdot 0.18\ CF_3CO_2H$ (488.818):

C, 52.48; H, 3.96; N, 2.86.

Found: C, 52.46; H, 4.03; N, 2.80.

EXAMPLE 1rr

3-Benzyloxycarbonylamino-5-[(5-methyl-naphthalen-1-yl)-acetoxy]-4-oxo-pentanoic acid, as a gray solid.

Analysis calculated for $C_{26}H_{25}NO_7 \cdot 0.20\ CF_3CO_2H$ (486.296):

C, 65.21; H, 5.22; N, 2.88.

Found: C, 65.21; H, 5.30; N, 2.88.

EXAMPLE 1ss

3-Benzyloxycarbonylamino-5-[(2-iodo-phenyl)-acetoxy]-4-oxo-pentanoic acid, as an off-white hygroscopic solid.

Analysis calculated for $C_{21}H_{20}INO_7$ (525.300):

C, 48.02; H, 3.84; N, 2.67.

Found: C, 48.33; H, 3.88; N, 2.66.

EXAMPLE 1tt

3-Benzyloxycarbonylamino-4-oxo-5-(3-pyridin-3-yl-propionyloxy)-pentanoic acid, trifluoroacetic acid salt as an off-white solid.

Analysis calculated for $C_{21}H_{22}N_2O_7 \cdot CF_3CO_2H$ (528.443):

C, 52.28; H, 4.39; N, 5.30.

Found: C, 52.26; H, 4.36; N, 5.19.

EXAMPLE 1uu

3-Benzyloxycarbonylamino-5-[(5-methoxy-naphthalen-1-yl)-acetoxy]-4-oxo-pentanoic acid, as a white solid.

Analysis calculated for $C_{26}H_{25}NO_8 \cdot 0.03\ CF_3CO_2H$ (482.912):

C, 64.82; H, 5.22; N, 2.90.

Found: C, 64.86; H, 5.22; N, 2.92.

EXAMPLE 1vv

3-Benzyloxycarbonylamino-5-[(8-methyl-naphthalen-1-yl)-acetoxy]-4-oxo-pentanoic acid, as a tan solid.

Analysis calculated for $C_{26}H_{25}NO_7 \cdot 0.2\ CF_3CO_2H$ (486.297):

C, 65.21; H, 5.22; N, 2.88.

Found: C, 65.16; H, 5.38; N, 2.73.

EXAMPLE 1ww

3-Benzyloxycarbonylamino-5-[(9H-fluoren-9-yl)-acetoxy]-4-oxo-pentanoic acid

MS (APCI) m/z 488.4 (M+1)

EXAMPLE 1xx

3-Benzyloxycarbonylamino-5-[(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-acetoxy]-4-oxo-pentanoic acid

MS (APCI) m/z 515.8 (M+1)

EXAMPLE 1yy

5-Oxo-1-(toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid 3-benzyloxycarbonylamino-4-carboxy-2-oxo-butyl ester

MS (APCI) m/z 547.3 (M+1)

EXAMPLE 1zz

5-Oxo-pyrrolidine-1,2-dicarboxylic acid 1-benzyl ester 2-(3-benzyloxycarbonyl-amino-4-carboxy-2-oxo-butyl) ester

MS (APCI) m/z 527.3 (M+1)

EXAMPLE 1aaa

1-Benzoyl-pyrrolidine-2-carboxylic acid 3-benzyloxycarbonylamino-4-carboxy-2-oxo-butyl ester

MS (APCI) m/z 483.0 (M+1)

EXAMPLE 1bbb

Pyrrolidine-1,2-dicarboxylic acid 1-benzyl ester 2-(3-benzyloxycarbonylamino-4-carboxy-2-oxo-butyl) ester

MS (APCI) m/z 469.1 (M-43)

EXAMPLE 1ccc

3-Benzyloxycarbonylamino-5-(2-benzyl-3-phenyl-propionyloxy)-4-oxo-pentanoic acid

MS (ESI) m/z 502.4 (M-H)

EXAMPLE 1ddd

3-Benzyloxycarbonylamino-5-[(5-cyano-naphthalen-1-yl)-acetoxy]-4-oxo-pentanoic acid, as a tan solid.

Analysis for $C_{26}H_{22}N_2O_7 \cdot 0.07\ CF_3CO_2H$ (482.456)

C, 65.08; H, 4.61; N, 5.81.

Found: C, 65.03; H, 4.79; N, 5.64.

EXAMPLE 1 eee

3-Benzyloxycarbonylamino-4-oxo-5-(3-phenyl-3-pyridin-3-yl-propionyloxy)-pentanoic acid as an orange solid.

Analysis calculated for $C_{27}H_{26}N_2O_7 \cdot 1.02\ CF_3CO_2H$ (606.822):

C, 57.48; H, 4.49; N, 4.62.

Found: C, 57.45; H, 4.69; N, 4.29.

EXAMPLE 1fff

3-Benzyloxycarbonylamino-4-oxo-5-(3-phenyl-3-pyridin-4-yl-propionyloxy)-pentanoic acid, as a tan solid.

Analysis calculated for $C_{27}H_{26}N_2O_7 \cdot 1.23\ CF_3CO_2H$ (630.767):

C, 56.10; H, 4.35; N, 4.44.

Found: C, 56.10; H, 4.50; N, 4.25.

EXAMPLE 1ggg

3-Benzyloxycarbonylamino-4-oxo-5-[(1-oxo-3,4-dihydro-1H-isoquinolin-2-yl)-acetoxy]-pentanoic acid

MS (ESI) m/z 469.1 (M+1). (1-Oxo-3,4-dihydro-1H-isoquinolin-2-yl)-acetic acid was prepared according to the procedure of W. K. Anderson, et al., J. Med. Chem., 1988;31:2097.

EXAMPLE 2

3-Benzenesulfonylamino-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid

Step A

A mixture of 3-benzyloxycarbonylamino-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid tert-butyl ester (1.495 g, 2.956 mmol, Example 1, Step A), 20% Pd/C (0.50 g) and concentrated hydrochloric acid (1.00 mL, 12.1 mmol) in 25 mL of ethanol was hydrogenated under balloon pressure at room temperature for 2 hours. The mixture was filtered through a pad of Celite, and the filtrate was

concentrated to give 3-amino-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid, tert-butyl ester hydrochloride as a foamy off-white solid.

Step B

To a solution at 0°C under nitrogen of 3-amino-5 (naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid, tert-butyl ester hydrochloride (0.239 g, 0.587 mmol, Example 2, Step A) in 10 mL of acetonitrile was added dropwise (via syringe) benzenesulfonyl chloride (0.075 mL, 0.588 mmol), followed by dropwise addition of 4-methylmorpholine (0.20 mL, 1.819 mmol). The solution was allowed to slowly warm to room temperature overnight. The solution was concentrated, redissolved into ethyl acetate and washed with saturated $NaHCO_3$, saturated KH_2PO_4 and brine solutions. The ethyl acetate extract was dried ($MgSO_4$), filtered, concentrated and chromatographed (silica gel, 80% hexanes-20% ethyl acetate) to give 3-benzenesulfonylamino-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid, tert-butyl ester as a light yellow oil.

Step C

A solution of 3-benzenesulfonylamino-5-(naphthalen-1-yl acetoxy)-4-oxo-pentanoic acid, tert-butyl ester (0.136 g, 0.266 mmol, Example 2, Step B) and 10 mL of trifluoroacetic acid in 20 mL of dichloromethane was stirred at room temperature for 1 hour. The solution was concentrated to give the titled compound as a foamy off-white solid.

Analysis calculated for $C_{23}H_{21}NO_7S \cdot 0.75H_2O$ (469.002):

C, 58.90; H, 4.84; N, 2.99.

Found: C, 58.94; H, 4.73; N, 3.02.

In a process analogous to Example 2, using the appropriately substituted isocyantes, appropriately substituted sulfonyl chlorides, appropriately substituted chloroformates, or appropriately substituted acid chlorides with 3-amino-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid, tert-butyl ester hydrochloride (Example 2, Step A), the corresponding compounds were prepared as follows:

EXAMPLE 2a

3-Methoxycarbonylamino-5-(naphthalene-1-yl-acetoxy)-4-oxo-pentanoic acid, as off-white solid.

Analysis calculated for $C_{19}H_{19}HO_7$ (373.366):

C, 61.12; H, 5.13; N, 3.75.

Found: C, 60.85; H, 5.25; N, 3.58.

EXAMPLE 2b

5-(Naphthalene-1-yl-acetoxy)-4-oxo-3-(3-phenyl-propionylamino)-pentanoic acid, as white solid.

Analysis calculated for $C_{26}H_{25}NO_6 \cdot 0.25H_2O$ (451.996):

C, 69.09; H, 5.69; N, 3.10.

Found: C, 69.06; H, 5.45; N, 2.91.

EXAMPLE 2c

3-Methoxycarbonylamino-4-oxo-5-phenoxyacetoxy-pentanoic acid, as foamy off-white solid.

Analysis calculated for $C_{15}H_{17}NO_8 \cdot 0.80NaHCO_3$ (406.510):

C, 46.68; H, 4.41; N, 3.45.

Found: C, 46.89; H, 4.44; N, 3.43.

EXAMPLE 2d

3-(2-Methanesulfonyl-ethanesulfonylamino)-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid, as a solid, mp 131-135°C.

Analysis calculated for $C_{20}H_{23}NO_9S_2$ (485.536):

C, 49.48; H, 4.78; N, 2.88.

Found: C, 49.26; H, 4.60; N, 2.88.

EXAMPLE 2e

3-(2-Methanesulfonyl-1-methyl-ethylsulfanylamino)-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid

Analysis calculated for $C_{21}H_{25}NO_9S_2 \cdot 1.0\ H_2O$ (517.578):

C, 48.73; H, 5.26; N, 2.71.

Found: C, 48.90; H, 5.60; N, 2.78.

EXAMPLE 3

[S-(R*,R*)]-3-(2-Acetylamino-propionylamino)-5-(naphthalene-1-yl-acetoxy)-4-oxo-pentanoic acid

Step A

To a solution at 0°C under nitrogen of N-acetyl alanine (0.176 g, 1.34 mmol), 3-amino-5-(naphthalene-1-yl-acetoxy)-4-oxo-pentanoic acid, tert-butyl ester, hydrochloride (0.500 g, 1.22 mmol, Example 2, Step A), 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (0.431 g, 1.34 mmol), 1-hydroxybenzotriazole (0.214 g, 1.58 mmol) in 15 mL of dichloromethane was added dropwise (via syringe) N,N-diisopropylethylamine (0.531 mL, 3.05 mmol). The solution was allowed to slowly warm to room temperature overnight. The solution was then dissolved in ethyl acetate and washed with 2× 5% citric acid solution, 2× saturated $NaHCO_3$, and 1× brine. The ethyl acetate extract was dried ($MgSO_4$), filtered, concentrated, and chromatographed (silica gel, 30% tetrahydrofuran-70% dichloromethane) to give [S-(R*,R*)]-3-(2-Acetylamino-propionylamino)-5-(naphthalene-1-yl-acetoxy)-4-oxo-pentanoic acid, tert-butyl ester as a light yellow thick oil.

Step B

A solution of [S-(R*,R*)]-3-(2-Acetylamino-propionylamino)-5-(naphthalene-1-yl-acetoxy)-4-oxo-pentanoic acid, tert-butyl ester (0.467 g, 0.96 mmol), and 7.5 mL of trifluoroacetic acid in 7.5 mL of dichloromethane was stirred at room temperature for 2 hours. The solution was concentrated and chromatographed (silica gel, 94% dichloromethane-5% methanol-1% acetic acid)

to give the title compound as an oily foam. The title compound was then lyophilized to a solid from acetonitrile and water.

^{1}H NMR (400 MHz, d_6DMSO), 12.43 (bs, 1H), 8.44 (d, 1H), 7.95 (m, 2H), 7.87 (m, 1H), 7.51 (m, 4H), 4.87 (m, 2H), 4.56 (m, 1H), 4.23 (s, 2H), 4.18 (m, 1H), 2.72 (dd, 1H), 2.54 (dd, 1H), 1.81 (s, 3H), 1.17 (d, 3H)

In a process analogous to Example 3, the corresponding compounds were prepared:

EXAMPLE 3a

5-(Naphthalen-1-yl-acetoxy)-4-oxo-3-[(thiophene-3-carbonyl)-amino]-pentanoic acid, as a foamy off-white solid.

Analysis calculated for $C_{22}H_{19}NO_6S \cdot 0.45\ H_2O$ (433.571):

C, 60.95; H, 4.63; N, 3.23.

Found: C, 60.98; H, 4.81; N, 3.29.

EXAMPLE 3b

3-[(Furan-3-carbonyl)-amino]-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid, as a white solid.

Analysis calculated for $C_{22}H_{19}NO_7 \cdot 0.25\ H_2O$ (413.903):

C, 63.84; H, 4.75; N, 3.38.

Found: C, 63.86; H, 4.50; N, 3.39.

EXAMPLE 3c

5-(Naphthalen-1-yl-acetoxy)-4-oxo-3-[2-(4-phenyl-butyrylamino)-propylamino]-pentanoic acid

MS(CI) m/z 533 (M+1)

EXAMPLE 3d

3-(2-Methanesulfonylamino-propionylamino)-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid

MS(APCI) m/z 465 (M+1)

EXAMPLE 3e

3-[2-(2-Acetylamino-4-phenyl-butyrylamino)-propionylamino]-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid

MS (APCI) m/z 590.4 (M+1)

EXAMPLE 3f

3-(2-Acetylamino-butyrylamino)-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid

MS (APCI) m/z 443.5 (M+1)

EXAMPLE 3g

3-[2-(4-Carbamoyl-butyrylamino)-propionylamino]-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid

MS (APCI) m/z 500.5 (M+1)

EXAMPLE 3h

3-(2-Benzyloxycarbonylamino-propionylamino)-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid

MS (APCI) m/z 521.4 (M+1)

EXAMPLE 3i

5-(Naphthalen-1-yl-acetoxy)-4-oxo-3-(2-ureido-propionylamino)-pentanoic acid

MS (APCI) m/z 430.5 (M+1)

EXAMPLE 3j

3-(2-Acetylamino-propionylamino)-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid

MS (APCI) m/z 429.5 (M+1)

EXAMPLE 3k

3-[(1-Acetyl-pyrrolidine-2-carbonyl)-amino]-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid

MS (APCI) m/z 455.5 (M+1)

EXAMPLE 3l

3-(2-Methyl-3-oxo-3-thiophen-2-yl-propionylamino)-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid

MS (APCI) m/z 482.4 (M+1)

EXAMPLE 3m

3-(2-Acetylamino-acetylamino)-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid

MS (APCI) m/z 415.5 (M+1)

EXAMPLE 3n

3-(2-Acetylamino-propionylamino)-5-(3,3-diphenyl-propionyloxy)-4-oxo-pentanoic acid

MS (APCI) m/z 469.2 (M+1)

EXAMPLE 3o

3-[2-(2-Acetylamino-4-carboxy-butyrylamino)-propionylamino]-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid

MS (APCI) m/z 596.1 (M-1)

Example 3p

5-(Naphthalen-1-yl-acetoxy)-4-oxo-3-[2-(3-phenyl-propionylamino)-propionylamino]-pentanoic acid

MS (APCI) m/z 518.8 (M+1)

EXAMPLE 3q

3-[2-(3-Methyl-butyrylamino)-propionylamino]-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid

MS (APCI) m/z 470.8 (M+1)

EXAMPLE 3r

3-[(1-Carbamoyl-pyrrolidine-2-carbonyl)-amino]-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid

EXAMPLE 3s

3-(3-Benzyloxy-2-ureido-propionylamino)-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid

EXAMPLE 3t

3-[(1-Acetyl-4-benzyloxy-pyrrolidine-2-carbonyl)-amino]-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid

EXAMPLE 3u

3-(4-Carbamoyl-butyrylamino)-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid

EXAMPLE 3v

3-(3-Carbamoyl-2-methyl-propionylamino)-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid

EXAMPLE 3w

3-[2-(1-Methyl-1H-imidazol-4-yl)-acetylamino]-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid

EXAMPLE 4

(S)-5-(Naphthalene-1-yl-acetoxy)-4-oxo-3-phenylacetylamino-pentanoic acid

Step A

To a solution at room temperature under nitrogen of phenylacetyl chloride (0.160 mL, 1.22 mmol), 3-amino-5-(naphthalene-1-yl-acetoxy)-4-oxo-pentanoic acid, tert-butyl ester, hydrochloride (0.500 g, 1.22 mmol, example 2, Step A), 4-dimethylaminopyridine (catalytic) in 25 mL of acetonitrile was added dropwise (via syringe) N,N-diisopropylethylamine (0.471 mL, 2.69 mmol). The solution was stirred overnight. The solution was then dissolved in ethyl acetate and washed

with 2× 5% citric acid solution, 2× saturated $NaHCO_3$, and 1× brine. The ethyl acetate extract was dried ($MgSO_4$), filtered, concentrated, and chromatographed (silica gel, 40% ethyl acetate-60% hexanes) to give (S)-5-(naphthalene-1-yl-acetoxy)-4-oxo-3-phenylacetylamino-pentanoic acid, tert-butyl ester as a thick oil.

Step B

(S)-5-(Naphthalene-1-yl-acetoxy)-4-oxo-3-phenylacetylamino-pentanoic acid, tert-butyl ester (0.300 g, 0.61 mmol, Example 4, Step A) and 7.5 mL of trifluoroacetic acid in 7.5 mL of dichloromethane was stirred at room temperature for 2 hours. The solution was concentrated and chromatographed (silica gel, 40% ethylacetate-59% hexanes-1% acetic acid) to give the title compound as an oily foam. The title compound was then lyophilized to a solid from acetonitrile and water.

^1H NMR (400 MHz, d_6DMSO), 12.49 (bs, 1H), 8.64 (bs, 1H), 7.94 (m, 2H), 7.84 (m, 1H), 7.49 (m, 4H), 7.27 (m, 5H), 4.85 (bs, 2H), 4.62 (m, 1H), 4.21 (s, 2H), 3.47 (s, 2H), 2.69 (dd, 1H), 2.59 (dd, 1H)

In a process analogous to Example 4, the corresponding compounds were prepared:

EXAMPLE 4a

(S)-5-(Naphthalene-1-yl-acetoxy)-4-oxo-3-(2-thiophene-2-yl-acetylamino)-pentanoic acid

^1H NMR (400 MHz, d_6DMSO), 12.52 (bs, 1H), 8.67 (bs, 1H), 7.89 (m, 3H), 7.49 (m, 4H), 7.34 (m, 1H), 6.93 (m, 2H), 4.88 (bs, 2H), 4.62 (m, 1H), 4.22 (s, 2H), 3.71 (s, 2H), 2.69 (dd, 1H), 2.60 (dd, 1H)

EXAMPLE 4b and 4c

3-[(2-Carbamoyl-cyclopentanecarbonyl)-amino]-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid, diastereomer A and B

Step A

To a solution of trans-2-carbamoyl-cyclopentanecarboxylic acid (130 mg, 0.83 mmol) and pyridine (65 mg, 0.83 mmol) in acetonitrile (100 mL) was added cyanuric fluoride (110 mg, 0.83 mmol) and the reaction mixture was stirred at room temperature for 3 hours. Ice water (10 mL) was added and the reaction mixture was stirred for 5 minutes. It was extracted with methylene chloride (75 mL) and the organic layer was evaporated to give the crude intermediate acid fluoride (50 mg). A solution of the acid fluoride in 1:1 methylene chloride:acetonitrile (20 mL) was treated with the hydrochloride salt of 3 amino-5-(naphthalene-1-yl-acetoxy) 4-oxo-pentanoic acid tert- butyl ester (100 mg, 0.25 mmol, Example 2, Step A) and N-methylmorpholine (0.5 mmol). The reaction mixture was stirred at room temperature for 2 hours followed by evaporation of the solvent. Purification by flash chromatography (silica gel, ethyl acetate) gave two diastereomers of 3-[(2-carbamoyl-cyclopentanecarbonyl)-amino]-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid tert-butyl ester [diastereomer A (high Rf) MS (AP+): 510.9 and diastereomer B(low Rf)] MS (APCI) m/z 510.9 (M+1).

Step B

Diastereomer A or B was reacted with trifluoroacetic acid as described for Example 4 to yield 3-[(2-carbamoyl-cyclopentanecarbonyl)-amino]-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid **4b** (diastereomer A), mp 171-185°C and 3-[(2-carbamoyl-cyclopentanecarbonyl)-amino]-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid **4c** (diastereomer B), mp 208-210°C.

EXAMPLE 4d

3-[(3-Carbamoyl-bicyclo[2.2.1]heptane-2-carbonyl)-amino]-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid

3-[(3-Carbamoyl-bicyclo[2.2.1]heptane-2-carbonyl)-amino]-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid tert-butyl ester was prepared by the method of Example 4b and 4c in 47% yield from (1R, 2S, 3S, 4S)-3-carbamoyl-2-carboxybicyclo[2.2.1]heptane (Ohtani, et al., JOC, 1991;562:122-2127).

EXAMPLE 4e

3-(3-Carbamoyl-2-methyl-propionylamino)-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid

Step A

To a solution of (S)-(-)-2-methylsuccinamic acid (0.160 g, 1.22 mmol, prepared according to the procedure in Chem. Pharm. Bull., 1991;39(10):2706-2708) in 25 mL of dichloromethane and 25 mL of tetrahydrofuran at -78°C was added N-methylpiperidine (0.163 mL, 1.34 mmol) followed by dropwise addition of isobutyl chloroformate (0.166 mL, 1.26 mmol). The reaction mixture was stirred for 1 hour at -78°C. A solution of 3-amino-5-(naphthalene-1-yl-acetoxy)-4-oxo-pentanoic acid tert-butyl ester, hydrochloride (0.500 g, 1.22 mmol, Example 2, Step A) in dichloromethane (25 mL) and tetrahydrofuran (25 mL) was added dropwise while simultaneously adding N-methylpiperidine (0.163 mL, 1.34 mmol) dropwise with a second addition funnel. The reaction mixture was allowed to slowly warm to room temperature and was stirred overnight. The reaction mixture was diluted with ethyl acetate was washed sequentially with 5% citric acid, saturated sodium bicarbonate, and finally with saturated sodium chloride. The organic layer was dried over magnesium sulfate, filtered and concentrated in vacuo. The resulting solid was suspended in diethyl ether, collected by filtration, washed with diethyl ether and dried under reduced pressure to yield 294 mg (49%) of the intermediate 3-(3-carbamoyl-2-methyl-propionylamino)-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid tert-butyl ester.

Step B

A solution of 3-(3-carbamoyl-2-methyl-propionylamino)-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid tert- butyl ester (0.150 g, 0.309 mmol, Example 4e, Step A) in 10 mL of 4N hydrochloric acid/dioxane was stirred at room temperature for 2 hours. The solution was concentrated and the product purified by reverse phase HPLC. Lyophilization from acetonitrile and water gave 3-(3-carbamoyl-2-methyl-propionylamino)-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid as a solid.

^{1}HNMR(400MHz, DMSO) 12.38 (bs,1H), 8.49 (d,1H), 7.88 (m,1H), 7.54(m,4H), 7.28 (s,1H), 6.76 (s,1H), 4.89 (s,2H), 4.46 (m,1H), 4.22 (s,2H), 2.71 (m,2H), 2.74 (m,1H), 2.32 (dd, 1H), 2.08 (dd, 1H), 0.98 (d,3H). MS (APCI) m/z 429.1 (M+H).

EXAMPLE 4f

3-(3-Methanesulfonyl-2-methyl-propionylamino)-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid

Part A

A solution of 2(S)-methyl -3-methylsulfonyl) propionic acid (250 mg, 1.5 mmol, prepared according to the procedure of Vazquez, M. L. , et al., [WO 94/10136]) in 10 mL of thionyl chloride was allowed to stirred at 55°C under N_2 for 2 hours. The solvent was removed under reduced pressure, washed with benzene and reconcentrated to give an off-white solid. The resultant solid was dissolved in 40 mL THF and N-methylmorpholine (300 mg, 3.0 mmol) and 4-dimethylaminopyridine (120 mg, 1.0 mmol.) added followed by 3 amino-5-(naphthalene-1-yl-acetoxy) 4-oxo-pentanoic acid tert butyl ester, hydrochloride (Example 2, Step A) (407 mg, 1.0 mmol) in a single portion. The mixture allowed to stir at room temperature for 16 hours. The solution was diluted with ethyl acetate and washed with saturated $NaHCO_3$, saturated $KHPO_4$ and brine solution, dried ($MgSO_4$), filtered, and concentrated. Medium pressure chromatography (silica gel, 75% hexanes-25% ethyl acetate to 60% hexanes-40% ethyl acetate) of the crude oil afforded [S-(R*,R*)]-3-(3-methanesulfonyl-2-methyl-propionylamino)-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid tert butyl ester.

Part B

A solution of [S-(R*,R*)]-3-(3-methanesulfonyl-2-methyl-propionylamino)-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid tert butyl ester (232 mg, 0.45 mmol.)and trifluoroacetic acid (5 mL, 0.065 mol) in 5 mL of dichloromethane was stirred at room temperature for 2 hours. The solution was concentrated in vacuo and suspended in water to give the title compound as a off-white solid.

Analysis calculated for $C_{22}H_{25}NO_8S \cdot H_2O$ (481.51):

C, 54.87; H, 5.65; N, 2.91.

Found: C, 54.78; H, 5.42; N, 2.78.

EXAMPLE 4g

3-(3-Benzenesulfonyl-2-methyl-propionylamino)-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid

Part A

To a solution of 2-methyl-3-(thiobenzene) propionic acid methyl ester (4 g, 19 mmol., prepared according to the procedure J. Org. Chem., 1981;46:235-9) in 100 mL of acetic acid was added sodium perborate (7.33 g, 47.6 mmol) and the mixture heated to 55°C for 17 hours. The reaction was poured into water, extracted with methylene chloride, washed with aqueous sodium bicarbonate, dried ($MgSO_4$) and concentrated to give of 2-methyl-3-(benzenesulfonyl) propionic acid methyl ester as a colorless oil.

Part B

To a solution of 2-methyl-3-(benzenesulfonyl) propionic acid methyl ester (4.47 g, 18.5 mmol) in 60 mL of THF was added a solution of lithium hydroxide (0.93 g, 22.2 mmol.) in water (30 mL). The solution was allowed to stir at room temperature for 16 hours and then acidified to pH 1 with 1N $KHSO_4$ and the solution extracted with ethyl acetate 3 times. The combined organic solution was dried ($MgSO_4$) and concentrated to give a colorless oil which solidified upon standing to give 2-methyl-3-(benzenesulfonyl) propionic acid.

Part C

A solution of 2-methyl-3-(benzenesulfonyl) propionic acid (300 mg, 1.3 mmol) in 10 mL of thionyl chloride was allowed to stir at 55°C under N_2 for 16 hours. The solvent was removed under reduced pressure washed with benzene and reconcentrated to give yellow oil. The resultant oil was dissolved in 40 mL THF and N-methylmorpholine (300 mg, 3.0 mmol) and 4-dimethylaminopyridine (120 mg, 1.0 mmol.) added followed by 3 amino-5-(naphthalene-1-yl-acetoxy) 4-oxo-pentanoic acid, tert-butyl ester, hydrochloride (407 mg, 1.0 mmol, Example

2, Step A) in a single portion. The mixture allowed to stir at room temperature for 36 hours. The solution was diluted with ethyl acetate and washed with saturated $NaHCO_3$, saturated $KHPO_4$ and brine solution, dried ($MgSO_4$), filtered, and concentrated. Medium pressure chromatography (silica gel, 75% hexanes-25% ethyl acetate to 60% hexanes-40% ethyl acetate) of the crude oil afforded 3-(3-benzenesulfonyl-2-methyl-propionylamino)-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid tert butyl ester.

Part D

A solution of 3-(3-benzenesulfonyl-2-methyl-propionylamino)-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid tert butyl ester (216 mg, mmol) and trifluoroacetic acid (5 mL, 0.065 mol) in 5 mL of dichloromethane was stirred at room temperature for 2 hours. The solution was concentrated in vacuo and suspended in ethyl ether to give the title compound as a off-white solid.

Analysis calculated for $C_{27}H_{27}NO_8S \cdot C_2HF_3O_2$ (611.10)

C, 56.01; H, 4.58; N, 2.29.

Found: C, 56.12; H, 4.86; N, 2.40.

In a process analogous to Example 4, the corresponding compounds were prepared:

EXAMPLE 4h

3-Butyrylamino-5-(naphthalen-2-yl-acetoxy)-4-oxo-pentanoic acid

MS (CI) m/z 386 (M+1)

EXAMPLE 4i

3-Acetylamino-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid as a foamy off-white solid.

Analysis calculated for $C_{19}H_{19}NO_6 \cdot H_2O$ (375.382):

C, 60.80; H, 5.64; N, 3.73.

Found: C, 61.07; H, 5.70; N, 3.57.

EXAMPLE 4j

3-(3-Methanesulfonyl-2-methyl-propionylamino)-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid

Analysis calculated for $C_{22}H_{25}NO_8S \cdot 1.0\ H_2O$ (481.526):

C, 54.88; H, 5.65; N, 2.91.

Found: C, 54.78; H, 5.42; N, 2.78.

EXAMPLE 4k

3-(3-Methyl-butyrylamino)-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid

MS (APCI) m/z 399.8 (M+1)

EXAMPLE 4l

3-(3-Carbamoyl-propionylamino)-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid

^1H NMR (400 Mhz, DMSO) 12.38 (bs,1H), 8.44 (d,1H), 7.93 (m,3H), 7.50(m,4H), 7.28 (s,1H), 6.75 (s,1H), 4.92 (dd,2H), 4.56 (m,1H), 4.23 (s,2H), 2.68 (dd,1H), 2.52 (dd,1H), 2.49 (m, 4H).

MS (APCI) m/z 415.5 (M+H)

EXAMPLE 4m

[S-(R*,R*)]-3-(3-Acetylsulfanyl-2-methyl-propionylamino)-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid

Analysis calculated for $C_{23}H_{25}NO_7S \cdot 0.1\ CF_3CO_2H$ (470.925):

C, 59.17; H, 5.37; N, 2.97.

Found: C, 59.39; H, 5.59; N, 3.01.

EXAMPLE 4n

trans-3-[(3-Carbamoyl-cyclopentanecarbonyl)-amino]-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid

Analysis calculated for $C_{24}H_{26}N_2O_7 \cdot 1.5\ H_2O$:

C, 59.86; H, 6.07; N, 5.82.

Found: C, 59.74; H, 5.80; N, 5.48.

EXAMPLE 5

3-(1,2,3,4-tetrahydro-1-oxo-isoquinoline-2-yl)-acetamino-5-(naphthalene-1-yl acetoxy)-4-oxo-pentanoic acid

Step A

To a solution of (1,2,3,4-tetrahydro-1-oxo-isoquinoline-2-yl)acetic acid (2.7 g, 13.0 mMol) prepared according to the procedure of Anderson W.K., et al., J. Med. Chem, 1988;31:2097 and H-Asp (OtBu)OMe•HCl (2.9 g, 12.0 mMol) in dimethylformamide (40 mL) was added at 0°C 1-ethyl-3-(3'-dimethylamino-propyl) carbodiimide × HC1 (2.5 g, 13.0 mMol) and triethylamine (4.05 g, 40 mMol). The mixture was stirred at room temperature for 16 hours. Most of the solvent was removed under reduced pressure, the residue was dissolved in ethyl acetate. The organic phase was washed successively with aqueous sodium hydrogen carbonate and water, dried over sodium sulfate, and concentrated to give 4.5 g of an amorphous residue.

The residue was dissolved in 40 mL of dioxane/water (1:1) and hydrolyzed in the presence of thymolphthalein by dropwise addition of 1N NaOH (12.0 mL). After evaporation of most of the dioxane and dilution with water the aqueous solution was extracted with ether, acidified with dilute HC1 to pH 2-3, and the product extracted into ethyl acetate. The organic phase was washed with water, dried over sodium sulfate, and concentrated under reduced pressure to give 3.4 g of crystalline N-(1,2,3,4-tetrahydro-1-oxo-isoquinoline-2-yl)-acetyl aspartic acid, 4-tert-butyl ester.

Step B

To a solution of N-(1,2,3,4-tetrahydro-1-oxo-isoquinoline-2-yl)-acetyl aspartic acid, 4-tert-butyl ester (2.8 g, 7.4 mMol) in tetrahydrofuran (40 mL) at -15°C was added N-methylmorpholine (0.75 mL, 8 mMol) followed by dropwise

addition of ethyl chloroformate (0.79 mL, 8 mMol). After 15 minutes at -10°C 50 mL of a 0.2N solution of diazomethane in ether was added dropwise. The reaction was kept for 2 hours at room temperature then 15 mL of a solution of 48% HBr in glacial acetic acid (1:1) was added dropwise at 0°C. After stirring for 15 minutes the reaction mixture was poured into ethyl acetate. The organic phase was washed successively with saturated aqueous sodium hydrogen carbonate and water, dried over sodium sulfate, and concentrated under reduced pressure to give 3-(1,2,3,4-tetrahydro-1-oxo-isoquinoline-2-yl)-acetamino-5-bromo-4-oxo-pentanoic acid, tert-butyl ester (3.1 g).

Step C

To a mixture of 3-(1,2,3,4-tetrahydro-1-oxo-isoquinoline-2-yl)-acetamino-5-bromo-4-oxo-pentanoic acid, tert-butyl ester (0.7 g, 1.5 mMol) and potassium fluoride (0.26 g, 4.5 mMol) in dimethylformamide (30 mL) was added 1-naphthylacetic acid (0.28 g, 1.5 mMol). The mixture was stirred at room temperature for 16 hours. Most of the solvent was evaporated under reduced pressure, the residue was partitioned between ethyl acetate and water. The organic phase was washed successively with aqueous sodium hydrogen carbonate and water, dried over sodium sulfate. Evaporation under reduced pressure followed by chromatography over silica (elution with dichloromethane/acetone 20:1) gave 0.31 g of 3-(1,2,3,4-tetrahydro-1-oxo-isoquinoline-2-yl)-acetamino-5-(naphthalene-1-yl acetoxy)-4-oxo-pentanoic acid, tert-butyl ester.

Step D

3-(1,2,3,4-tetrahydro-1-oxo-isoquinoline-2-yl)-acetamino-5-(naphthalene-1-yl acetoxy)-4-oxo-pentanoic acid, tert-butyl ester (0.28 g, 0.5 mMol) in 20 mL of a 1:1 mixture of dichloromethane/trifluoroacetic acid was stirred at room temperature for 45 minutes. Evaporation under reduced pressure followed by crystallization from dichloromethane/ether/hexane gave 3-(1,2,3,4-tetrahydro-1-oxo-isoquinoline-2-yl)-acetamino-5-(naphthalene-1-yl acetoxy)-4-oxo-pentanoic acid (0.19 g).

m. p. 117°C-124°C; NMR (d_6-DMSO, ppm): 12.5 (bs, 1H), 8.5 (d, 1H), 8.1-7.8 (M, 4H), 7.6-7.4 (m, 5H), 7.4-7.2 (m, 2H), 5.0 (m, 2H), 4.65 (dd, 1H), 4.25 (s, 2H), 4.18 (dd, 2H), 3.6 (m, 2H), 3.0 (m, 2H), 2.75-2.5 (2m, 2H).

EXAMPLE 5a

3-(2-Methyl-3-phenethylcarbamoyl-propionylamino)-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid

Step A

A solution of itaconic anhydride (5.00g, 44.6 mmol) and phenethylamine (5.95 g, 49.1 mmol) in 100 mL of acetonitrile was stirred at room temperature under nitrogen for 72 hours. The mixture (solid had formed) was concentrated, then partitioned between EtOAc and 1N HCl. The organic extract was washed with brine, dried ($MgSO_4$), concentrated and the residue was crystallized from diethyl ether to give 5.24 g (50%) of 2-(phenethylcarbamoyl-methyl)-acrylic acid as a white solid: mp 133-140°C.

Analysis calculated for $C_{13}H_{15}NO_3$ (233.269):

C, 66.94; H, 6.48; N, 6.00.

Found: C, 66.74; H, 6.56; N, 6.00.

Step B

A solution of 2-(phenethylcarbamoyl-methyl)-acrylic acid (2.76 g, 11.8 mmol, Step A) in 100 mL of THF was treated with 5% Pd/C (0.2 g) and hydrogenated at room temperature and 52 psi of hydrogen for 2.5 hours. The mixture was filtered and concentrated to give 2.39 g (86%) of 2-(phenethylcarbamoyl-methyl)-propionic acid as an off-white solid.

Analysis calculated for $C_{13}H_{17}NO_3$ (235.285):

C, 66.36; H, 7.28; N, 5.95.

Found: C, 65.31; H, 7.05; N, 5.80.

Step C

A mixture of 2-(phenethylcarbamoyl-methyl)-propionic acid (1.63 g, 6.93 mmol, Step B), H-Asp(OtBu)-OMe•HCl (1.83 g, 7.64 mmol, purchased from Bachem Bioscience Inc.), 1-hydroxybenzotriazole hydrate (1.17 g, 7.64 mmol), N-ethyl-N'-(3-dimethylaminopropyl)-carbodiimide hydrochloride (1.46 g, 7.62 mmol) and 4-methylmorpholine (0.95 mL, 8.64 mmol) in 100 mL of dichloromethane was stirred at room temperature for 24 hours. The mixture was concentrated, then partitioned between EtOAc and saturated $NaHCO_3$ solution. The organic extract was washed with saturated KH_2PO_4 and brine solutions, dried ($MgSO_4$), filtered, concentrated, and chromatographed (silica gel, 25% hexanes-75% EtOAc) to give 2.54 g (87%) of 2-(2-methyl-3-phenethylcarbamoyl-propionylamino)-succinic acid, 4-tert-butyl ester 1-methyl ester as a waxy white solid.

Analysis calculated for $C_{22}H_{32}N_2O_6$ (420.510):

C, 62.84; H, 7.67; N, 6.66.

Found: C, 62.68; H, 7.69; N, 6.54.

Step D

A solution of 2-(2-methyl-3-phenethylcarbamoyl-propionylamino)-succinic acid, 4-tert-butyl ester 1-methyl ester (2.11 g, 5.01 mmol, Step C) and 0.1N sodium hydroxide solution (60.1 mL, 6.01 mmol) in 60 mL of ethanol was stirred at room temperature for 12 hours. The solution was concentrated, acidified with saturated KH_2PO_4 solution to a pH ~5 and extracted with chloroform (2 x 100 mL). The combined chloroform extract was dried ($MgSO_4$), filtered and concentrated to give 2.23 g (~100%) of 2-(2-methyl-3-phenethylcarbamoyl-propionylamino)-succinic acid, 4-tert-butyl ester as a colorless oil, which was used without further purification.

A solution of 2-(2-methyl-3-phenethylcarbamoyl-propionylamino)-succinic acid, 4-tert-butyl ester (2.23 g, 5.49 mmol) and 4-methylmorpholine (0.61 mL, 5.73 mmol) in 50 mL of THF in a Clear-Seal joint 250-mL round-bottom flask was cooled to ca. -45°C (Dry Ice-acetonitrile slurry) and treated with

isobutyl chloroformate (0.75 mL, 5.78 mmol). Solid immediately formed, the mixture was stirred for 15 minutes, then treated with a 0.5 M diazomethane in ether solution (55 mL, 27.5 mmol, generated from Diazald). The cooling bath was removed, the light yellow solution was stirred at room temperature for 2 hours, cooled to 0°C and treated dropwise with a solution of 48% hydrobromic acid (10 mL, 184 mmol) in 10 mL of acetic acid. The colorless solution was stirred at room temperature for 30 minutes, then partitioned between EtOAc and water (~200 mL of each). The organic extract was washed with water, saturated $NaHCO_3$ and brine solutions, dried ($MgSO_4$), filtered, and concentrated to give 1.40 g (53%) of 2-(2-methyl-3-phenethylcarbamoyl-propionylamino)-5-bromo-4-oxo-pentanoic acid, tert-butyl ester as a light yellow solid.

Step E

A mixture of 2-(2-methyl-3-phenethylcarbamoyl-propionylamino)-5-bromo-4-oxo-pentanoic acid, tert-butyl ester (0.70 g, 1.45 mmol, Step D), 1-naphthylacetic acid (0.34 g, 1.81 mmol) and potassium fluoride (0.21 g, 3.61 mmol) in 2.5 mL of DMF was stirred at room temperature for 12 hours. The sample was partitioned between EtOAc and saturated $NaHCO_3$ solution. The organic extract was washed with saturated KH_2PO_4 and brine solutions, dried ($MgSO_4$), filtered, and concentrated. The residue was chromatographed (silica gel, 25% hexanes-75% EtOAc) to give 0.65 g (77%) of 3-(2-methyl-3-phenethylcarbamoyl-propionylamino)-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid, tert-butyl ester.

Step F

A solution of 3-(2-methyl-3-phenethylcarbamoyl-propionylamino)-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid, tert- butyl ester (0.62 g, 1.06 mmol, Step E) and trifluoroacetic acid (5 mL) in 20 mL of dichloromethane was stirred at room temperature for 1 hour, then concentrated to a yellow oil. The sample was partitioned between EtOAc and saturated KH_2PO_4 solution. The organic extract was washed with brine, dried ($MgSO_4$), filtered, and concentrated

to 0.51 g (91%) of 3-(2-methyl-3-phenethylcarbamoyl-propionylamino)-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid as a white solid.

Analysis calculated for $C_{30}H_{32}N_2O_7 \cdot 1/3\ H_2O$ (538.604):

C, 66.90; H, 6.11; N, 5.20.

Found: C, 66.90; H, 6.14; N, 5.10.

In a process analogous to Example 5, the corresponding compounds were prepared:

EXAMPLE 5b

5-(Naphthalen-2-yl-acetoxy)-4-oxo-3-[2-(2-oxo-6-phenyl-piperidin-1-yl)-acetylamino]-pentanoic acid (as a mixture of diastereomers):

^1H NMR (d_6-DMSO): δ12.5 (1H, s), 8.38 (1H, 2d), 7.90-7.75 (4H, m), 7.50-7.10 (8H, m), 4.90 (2H, dd), 4.70-4.50 (2H, m), 4.40 (1H, m), 3.90 (2H, s), 3.0 (1H, dd), 2.7 (1H, m), 2.40-2.30 (2H, m), 2.20 (1H, m) 1.8-1.5 (4H, m). The starting acid, 6-phenyl-piperidine-2-one, was prepared according to the procedure of L.D. Desaubry, C.G. Wermuth and J.J. Bourguignon, Tetrahedron Lett., 1995;36:4249, then alkylation with ethyl bromoacetate (NaH/toluene; 1 hour at 110°C) followed by alkaline hydrolysis.

EXAMPLE 5c

5-(Naphthalen-1-yl-acetoxy)-4-oxo-3-[2-(2-oxo-6-phenyl-piperidin-1-yl)-acetylamino]-pentanoic acid (as a mixture of diastereomers):

^1H NMR (d_6-DMSO): δ13.0-12.0 (1H, bs), 8.4 (1H, m), 8.1-7.8 (3H, m), 7.6-7.0 (9H, m), 5.05-4.8 (2H, m), 4.70-4.50 (2H, m), 4.45-4.35 (1H, m), 4.25 (2H, s), 3.0 (1H, m), 2.7 (1H, m), 2.5 (DMSO + 1H, m), 2.40 (2H, m), 2.10 (1H, m) 1.8-1.5 (3H, m). The starting acid, 6-phenyl-piperidine-2-one, was prepared as described for Example 5b.

EXAMPLE 5d

3-[3-Methyl-2-(3-phenyl-propionylamino)-butyrylamino]-4-oxo-5-[(1-oxo-1,2,3,4-tetrahydro-naphthalen-2-yl)-acetoxy]-pentanoic acid

MS (ESI) m/z 565.2 (M+1)

EXAMPLE 5e

5-(Naphthalen-2-yl-acetoxy)-4-oxo-3-[2-(1-oxo-3,4-dihydro-1H-isoquinolin-2-yl)-acetylamino]-pentanoic acid

^{1}H NMR (d_6-DMSO): δ12.5 (1H, m) 8.6 (1H, d), 8.0-7.8 (5H, m), 7.55-7.25 (6H, 2m), 4.95 (2H, dd), 4.65 (1H, dd), 4.15 (2H, s), 3.95 (2H, s), 3.55 (2H, dd), 3.0 (2H, m), 2.75 (1H, dd), 2.6 (1H, m). The starting acid, 1-oxo-3,4-dihydro-1H-isoquinolin-2-yl)-acetic acid, was prepared as described for Example 5.

EXAMPLE 5f

5-(2-Benzyl-3-phenyl-propionyloxy)-4-oxo-3-[2-(1-oxo-3,4-dihydro-1H-isoquinolin-2-yl)-acetylamino]-pentanoic acid

MS (ESI) m/z 557.2 (M+1)

The starting acid, (1-oxo-3,4-dihydro-1H-isoquinolin-2-yl)-acetic acid, was prepared as described for Example 5.

EXAMPLE 5g

5-(2-Benzyl-3-phenyl-propionyloxy)-4-oxo-3-[2-(2-oxo-6-phenyl-piperidin-1-yl)-acetylamino]-pentanoic acid (as a mixture of diastreomers)

^{1}H NMR (d_6-DMSO): δ12.5 (1H, bs), 8.35 (1H, 2d), 7.4-7.1 (15H, m), 4.75 (2H, dd), 4.6 (2H, m), 4.40 (1H, m), 3.1-2.5 (8H, m), 2.35 (2H, m), 2.10 (1H, m) 1.8-1.5 (3H, m). The starting acid, 6-phenyl-piperidine-2-one, was prepared as described for Example 5b.

EXAMPLE 5h

5-(Naphthalen-1-yl-acetoxy)-4-oxo-3-[2-(1-oxo-1,2,3,4-tetrahydro-naphthalen-2-yl)-acetylamino]-pentanoic acid

MS (ESI) m/z 483.5 (M-H_2O). The starting acid, (1-oxo-3,4-dihydro-1H-isoquinolin-2-yl)-acetic acid, was prepared as for Example 5.

EXAMPLE 5i

5-(Naphthalen-1-yl-acetoxy)-4-oxo-3-[2-(1-oxo-3,4-dihydro-1H-isoquinolin-2-yl)-propionylamino]-pentanoic acid

MS (ESI) m/z 517.4 (M+1). The starting acid, 2-(1-oxo-3,4-dihydro-1H-isoquinolin-2-yl)-propionic acid, was prepared in analogy to the literature procedure of Example 5, starting from ethyl 2-bromopropionate.

EXAMPLE 5j

5-(Naphthalen-2-yl-acetoxy)-4-oxo-3-[2-(1-oxo-3,4-dihydro-1H-isoquinolin-2-yl)-propionylamino]-pentanoic acid

MS (ESI) m/z 517.3 (M+1). The starting acid, 2-(1-oxo-3,4-dihydro-1H-isoquinolin-2-yl)-propionic acid, was prepared as described for Example 5i.

EXAMPLE 5k

3-[4-(1-Benzenesulfonyl-1H-pyrrol-2-yl)-4-oxo-butyrylamino]-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid

MS (ESI) m/z 605.4 (M+1). The starting acid, 4-(1-benzenesulfonyl-1H-pyrrol-2-yl)-4-oxo-butyric acid, was prepared as described according to the procedure of M. Kakushima,et al., J. Org. Chem., 1983;48: 3214.

EXAMPLE 5l

5-(2-Benzyl-3-phenyl-propionyloxy)-4-oxo-3-[2-(1-oxo-1,2,3,4-tetrahydro-naphthalen-2-yl)-acetylamino]-pentanoic acid

MS (ESI) m/z 556.4 (M+1). The starting acid, (1-oxo-3,4-dihydro-1H-isoquinolin-2-yl)-acetic acid, was prepared as described for Example 5.

EXAMPLE 5m

5-(2-Benzyl-3-phenyl-propionyloxy)-4-oxo-3-[2-(1-oxo-3,4-dihydro-1H-isoquinolin-2-yl)-propionylamino]-pentanoic acid (as a mixture of diastreomers):

^{1}H NMR (d_6-DMSO): δ12.5 (1H, m), 8.5 (1H, m), 7.9 (1H, m), 7.45-7.10 (13H, m), 5.2 (1H, m), 4.8 (2H, m), 4.65 (2H, m), 3.55 (2H, m), 3.1-2.65 (9H, m), 1.3 (3H, d). The starting acid, 2-(1-oxo-3,4-dihydro-1H-isoquinolin-2-yl)-propionic acid, was prepared as described as described for Example 5i.

EXAMPLE 5n

4-Oxo-3-[2-(1-oxo-3,4-dihydro-1H-isoquinolin-2-yl)-propionylamino]-5-[(1-oxo-1,2,3,4-tetrahydro-naphthalen-2-yl)-acetoxy]-pentanoic acid (as a mixture of diastreomers):

^{1}H NMR (d_6-DMSO): δ12.5 (1H, s), 8.6-8.5 (1H, 2d), 7.9 (2H, m), 7.6-7.2 (6H, m), 5.3-5.1 (1H, m), 4.9 (2H, s), 4.7 (1H, m), 3.45 (2H, m), 3.2-2.5 (9H, m), 2.2 (1H, m), 1.95 (1H, m), 1.3 (3H, d). The starting acid, 2-(1-oxo-3,4-dihydro-1H-isoquinolin-2-yl)-propionic acid, was prepared as described for Example 5i.

EXAMPLE 5o

3-[4-(1-Benzenesulfonyl-1H-pyrrol-2-yl)-4-oxo-butyrylamino]-5-(2-benzyl-3-phenyl-propionyloxy)-4-oxo-pentanoic acid

MS (ESI) m/z 659.4 (M+1). The starting acid, 4-(1-benzenesulfonyl-1H-pyrrol-2-yl)-4-oxo-butyric acid, was prepared as described for Example 5k.

EXAMPLE 5p

4-Oxo-5-[(1-oxo-1,2,3,4-tetrahydro-naphthalen-2-yl)-acetoxy]-3-[2-(1-oxo-1,2,3,4-tetrahydro-naphthalen-2-yl)-acetylamino]-pentanoic acid

MS (ESI) m/z 520.2 (M+1). The starting acid, (1-oxo-3,4-dihydro-1H-isoquinolin-2-yl)-acetic acid, was prepared as described for Example 5.

EXAMPLE 5q

5-(Naphthalen-1-yl-acetoxy)-4-oxo-3-[2-(2-oxo-3-phenyl-imidazolidin-1-yl)-propionylamino]-pentanoic acid

MS (ESI) m/z 518.2 (M+1). The starting acid, 2-(2-oxo-3-phenyl-imidazolidin-1-yl)-propionic acid, was prepared according to the procedure of Basha (see Example 5s) followed by alkylation and subsequent alkaline hydrolysis.

EXAMPLE 5r

5-(Naphthalen-1-yl-acetoxy)-4-oxo-3-[2-(2-oxo-3-phenyl-tetrahydro-pyrimidin-1-yl)-propionylamino]-pentanoic acid

MS (ESI) m/z 546.3 (M+1). The starting acid, 2-(2-oxo-3-phenyl-tetrahydro-pyrimidin-1-yl)-propionic acid was prepared from 2-oxo-3-phenyl-tetrahydro pyrimidine (see Basha, Example 5s) followed by alkylation with ethyl 2-bromo-propionate and subsequent alkaline hydrolysis.

EXAMPLE 5s

5-(Naphthalen-1-yl-acetoxy)-4-oxo-3-[2-(2-oxo-3-phenyl-tetrahydro-pyrimidin-1-yl)-acetylamino]-pentanoic acid

MS (ESI) m/z 532.3 (M+1). 1-Phenyl-tetrahydropyrimidine-2-one was prepared according to the procedure of A. Basha, Tetrahedron Lett., 1988;29:2525 followed by alkylation with ethyl bromoacetate (NaH/DMF; 16 hours at room temp.) and subsequent alkaline hydrolysis.

EXAMPLE 5t

3-(2-Acetylamino-3-methyl-butyrylamino)-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid

MS (ESI)m/z 455.3 (M-H).

EXAMPLE 5u

3-(2-Acetylamino-3-methyl-butyrylamino)-5-(2-benzyl-3-phenyl-propionyloxy)-4-oxo-pentanoic acid

MS (ESI) m/z 511.3 (M+1).

EXAMPLE 5v

3-(2-Acetylamino-3-methyl-butyrylamino)-5-(3-benzyl-4-phenyl-butyryloxy)-4-oxo-pentanoic acid

MS (ESI) m/z 525.3 (M+1).

EXAMPLE 5w

3-(2-Acetylamino-3-methyl-butyrylamino)-5-(4-benzyl-5-phenyl-pentanoyloxy)-4-oxo-pentanoic acid

MS (ESI) m/z 537.3 (M-1).

EXAMPLE 5x

3-(2-Acetylamino-3-methyl-butyrylamino)-4-oxo-5-[(1-oxo-1,2,3,4-tetrahydro-naphthalen-2-yl)-acetoxy]-pentanoic acid

MS (ESI) m/z 475.3 (M+1).

EXAMPLE 5y

5-(3-Benzyl-4-phenyl-butyryloxy)-3-[3-methyl-2-(3-phenyl-propionylamino)-butyrylamino]-4-oxo-pentanoic acid

MS (ESI) m/z 601.3 (M+1).

EXAMPLE 5z

3-[2-(3-Acetylamino-2-oxo-2H-pyridin-1-yl)-acetylamino]-5-(3,3-diphenyl-propionyloxy)-4-oxo-pentanoic acid as a course pink powder. The starting acid was prepared as described in Bioorganic & Medicinal Chemistry Letters, 1997;7:1337-1342.

Analysis calculated for $C_{29}H_{29}N_3O_8 \cdot 0.585\ CF_3CO_2H$ (614.274):

C, 58.99; H, 4.86; N, 6.84.

Found: C, 59.38; H, 5.16; N, 6.20.

EXAMPLE 5aa

3-[2-(3-Acetylamino-2-oxo-2H-pyridin-1-yl)-acetylamino]-5-(2-benzyl-3-phenyl-propionyloxy)-4-oxo-pentanoic acid as a fine brown powder. The starting acid was prepared as described in Bioorganic & Medicinal Chemistry Letters, 1997;7:1337-1342.

Analysis calculated for $C_{30}H_{31}N_3O_8 \cdot 0.468\ CF_3CO_2H$ (614.960):

C, 60.42; H, 5.16; N, 6.83.

Found: C, 60.82; H, 5.39; N, 6.42.

EXAMPLE 6

3-[2-(2-Benzyloxycarbonylamino-4-carboxy-butyrylamino)-3-methyl-butyrylamino]-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid

Step A

A mixture of HCl•H-Asp (OtBu)-OMe (13.1 g, 54.6 mmol), Z-Val-OH (15.1 g, 60.1 mmol), HOBT•H_2O (9.2 g, 60.0 mmol), 1-ethyl-3-(3′-dimethylaminopropyl)carbodiimide hydrochloride (EDCI•HCl, 11.5 g, 60.0 mmol) and 4-methylmorpholine (7.5 mL, 68.2 mmol) in 500 mL of dichloromethane was stirred at room temperature under nitrogen for 12 hours. The mixture was concentrated, then partitioned between ethyl acetate and sat. $NaHCO_3$ solution. The organic extract was washed with sat. KH_2PO_4 and brine solutions, dried ($MgSO_4$), filtered and concentrated to give 23.9 g (~100%) of 2-(2-benzyloxy-carbonylamino-3-methyl-butyrylamino)-succinic acid 4-tert-butyl ester 1-methyl ester as a white solid. MS (APCI) m/z (rel intensity) 436.9 (M+, 100), 380.9 (M-56, 94).

Step B

A solution of 2-(2-benzyloxycarbonylamino-3-methyl-butyrylamino)-succinic acid 4-tert-butyl ester 1-methyl ester (23.8 g, 54.5 mmol, Example 6, Step A) and concentrated hydrochloric acid (5.0 mL, 60.5 mmol) in 600 mL of EtOH:THF (5:1) was treated with 20% Pd/C (2.0 g) and hydrogenated at room temperature, 50 psig H_2 for 1.2 hours. The sample was filtered and concentrated. The resultant oily solid was washed with diethyl ether, filtered and vacuum dried to give 16.5 g of 2-(2-amino-3-methyl-butyrylamino)-succinic acid 4-tert-butyl ester 1-methyl ester, hydrochloride as a white solid, mp 166-167°C.

MS(APCI) m/z (rel intensity) 302.1 (M, 20), 301.1 (M-1, 100).

Analysis calculated for $C_{14}H_{26}N_2O_5$•HCl (338.835):

C, 49.63; H, 8.03; N, 8.27.

Found: C, 49.62; H, 8.19; N, 8.21.

Step C

A mixture of HCl•H-ValAsp (OtBu)-OMe (2-(2-amino-3-methyl-butyrylamino)-succinic acid 4-tert-butyl ester 1-methyl ester, hydrochloride, 15.4 g, 45.6 mmol, Example 6, Step B), Z-Glu(OtBu)-OH (15.8 g, 46.9 mmol), HOBT•H_2O (7.7 g, 50.1 mmol), EDCI•HCl (9.6 g, 50.1 mmol) and 4-methylmorpholine (6.3 mL, 57.3 mmol) in 500 mL of dichloromethane was stirred at room temperature under nitrogen for 12 hours. The mixture was concentrated, then partitioned between ethyl acetate and sat. $NaHCO_3$ solution. The organic extract was washed with sat. KH_2PO_4 and brine solutions, dried ($MgSO_4$), filtered and concentrated to give 26.3 g (93%) of Z-Glu(OtBu)ValAsp(OtBu)-OMe [2-[2-(2-benzyloxycarbonylamino-4-tert-butoxycarbonyl-butyrylamino)-3-methyl-butyrylamino]-succinic acid 4-tert-butyl ester 1-methyl ester] as a white solid. MS(APCI) m/z (rel intensity) 622.0 (M, 100), 565.9 (M-56, 68).

Analysis calculated for $C_{31}H_{47}N_3O_{10}$ (621.734):

C, 59.89; H, 7.62; N, 6.76.

Found: C, 59.88; H, 7.63; N, 6.70.

Step D

A solution of Z-Glu(OtBu)ValAsp(OtBu)-OMe (17.2 g, 27.6 mmol, Example 6, Step C) and 0.1N sodium hydroxide (330 mL, 33.0 mmol) in 300 mL of ethanol was stirred at room temperature under nitrogen for 1 hour. The slightly cloudy solution was concentrated (to remove most of the ethanol), acidified with saturated KH_2PO_4 solution to a pH ~5 and extracted twice with 500 mL of chloroform:methanol (9:1). The combined organic extract was dried ($MgSO_4$), filtered, and concentrated to give 15.0 g (89%) of Z-Glu(OtBu)ValAsp(OtBu)-OH as a foamy white solid.

Analysis calculated for $C_{30}H_{45}N_3O_{10}$ (607.707):

C, 59.29; H, 7.46; N, 6.91.

Found: C, 59.26; H, 7.57; N, 6.54.

Step E

A solution of Z-Glu(OtBu)ValAsp(OtBu)-OH (14.9 g, 24.6 mmol) and 4-methylmorpholine (2.7 mL, 24.6 mmol) in 200 mL of THF at ca. -40 °C (Dry Ice- CH_3CN bath) was treated with iso-butyl chloroformate (3.2 mL, 24.6 mmol). Solid immediately formed. The sample was stirred for 15 minutes, then treated with cold diazomethane (300 mL of an ether solution, freshly prepared for Diazald). The sample was stirred at room temperature for 2 hours, cooled to 0°C and quenched by dropwise addition of a 48% hydrobromic acid-acetic acid solution (35 mL of each). The ice-bath was removed, the sample was stirred at room temperature for 30 minutes, then extracted with ethyl acetate-water (500 mL of each). The organic extract was washed with water, sat. $NaHCO_3$ and brine solutions, dried ($MgSO_4$), filtered, and concentrated. The residue was crystallized from dichloromethane-hexanes to give 10.5 g (63%) of 3-[2-(2-benzyloxycarbonylamino-4-tert-butoxycarbonyl-butyrylamino)-3-methyl-butyrylamino]-5-bromo-4-oxo-pentanoic acid tert-butyl ester (Z-Glu(OtBu)ValAsp(OtBu)CH_2Br) as a white solid.

Analysis calculated for $C_{31}H_{46}BrN_3O_9$ (684.636):

C, 54.39; H, 6.77; N, 6.14.

Found: C, 54.24; H, 6.63; N, 6.08.

Step F

A mixture of Z-Glu(OtBu)ValAsp(OtBu)CH_2Br (9.4 g, 13.8 mmol, Example 6, Step E), 1-naphthylacetic acid (3.2 g, 17.2 mmol) and potassium fluoride (2.0 g, 34.4 mmol) in 20 mL of DMF was stirred at room temperature for 12 hours. The mixture was partitioned between ethyl acetate and saturated $NaHCO_3$ solution. The organic extract was washed with sat. KH_2PO_4 and brine solutions, dried ($MgSO_4$), filtered and concentrated to give 3-[2-(2-benzyloxy-carbonylamino-4-tert-butoxycarbonyl-butyrylamino)-3-methyl-butyrylamino]-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid tert-butyl ester as a white solid, mp 92-105°C.

Analysis calculated for $C_{43}H_{55}N_3O_{11}$ (789.931):

C, 65.38; H, 7.02; N, 5.32.

Found: C, 65.13; H, 7.20; N, 5.36.

Step G

A solution of 3-[2-(2-benzyloxycarbonylamino-4-tert-butoxycarbonyl-butyrylamino)-3-methyl-butyrylamino]-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid tert-butyl ester (1.0 g, 1.27 mmol, Example 6, Step F) and 10 mL of trifluoroacetic acid in 20 mL of dichloromethane was stirred at room temperature for 1 hour. The solution was concentrated to a light yellow oil. Ether (~50 mL) was added and the oil slowly solidified. The mixture was filtered and vacuum dried to give 0.81 g (95%) of 3-[2-(2-benzyloxycarbonylamino-4-carboxy-butyrylamino)-3-methyl-butyrylamino]-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid as a white solid.

Analysis calculated for $C_{35}H_{39}N_3O_{11}\cdot 0.70\ H_2O$ (690.325):

C, 60.90; H, 5.90; N, 6.09.

Found: C, 60.90; H, 5.90; N, 6.30.

In a process analogous to Example 6, the corresponding compounds were prepared:

EXAMPLE 6a

3-[2-(2-Benzyloxycarbonylamino-3-methyl-butyrylamino)-propionylamino]-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid as a white solid, mp 160-163°C.

Analysis calculated for $C_{33}H_{37}N_3O_9\cdot 0.50\ H_2O$ (628.685):

C, 63.05; H, 6.09; N, 6.68.

Found: C, 63.13; H, 5.96; N, 6.68.

EXAMPLE 6b

3-(2-Acetylamino-3-methyl-butyrylamino)-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid

MS (APCI) m/z 457.5 (M+1)

EXAMPLE 6c

3-[2-(2-Benzyloxycarbonylamino-3-methyl-butyrylamino)-propionylamino]-5-(3,3-diphenyl-propionyloxy)-4-oxo-pentanoic acid as a white solid,

mp 99-104°C.

Analysis calculated for $C_{36}H_{41}N_3O_9$ (659.743):

C, 65.54; H, 6.26; N, 6.37.

Found: C, 65.25; H, 6.23; N, 6.25.

EXAMPLE 6d

3-(2-Benzyloxycarbonylamino-3-methyl-naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid

MS (APCI) m/z 549.0 (M+1)

EXAMPLE 6e

3-[2-(2-Benzyloxycarbonylamino-4-carboxy-butyrylamino)-3-methyl-butyrylamino]-5-(2-benzyl-3-phenyl-propionyloxy)-4-oxo-pentanoic acid as white solid.

Analysis calculated for $C_{39}H_{45}N_3O_{11}\cdot 0.50\ H_2O$ (740.815):

C, 63.23; H, 6.26; N, 5.67.

Found: C, 63.14; N, 6.16; N, 5.55.

EXAMPLE 6f

3-[2-(2-Benzyloxycarbonylamino-3-methyl-butyrylamino)-propionylamino]-5-(2-benzyl-3-phenyl-propionyloxy)-4-oxo-pentanoic acid as a white solid.

Analysis calculated for $C_{37}H_{43}N_3O_9 \cdot 0.13\ CF_3CO_2H$ (688.593):

C, 64.99; H, 6.31; N, 6.10.

Found: C, 64.98; H, 6.50; N, 6.10.

EXAMPLE 6g

3-[2-(2-Benzyloxycarbonylamino-3-methyl-butyrylamino)-propionylamino]-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid as a white solid.

Analysis calculated for $C_{33}H_{37}N_3O_9 \cdot 0.25\ CF_3CO_2H$ (648.184):

C, 62.08; H, 5.79; N, 6.48.

Found: C, 62.07; H, 5.85; N, 6.68.

EXAMPLE 6h

3-(2-{2-[2-Acetylamino-3-(4-hydroxy-phenyl)-propionylamino]-4-carboxy-butyrylamino}-3-methyl-butyrylamino)-5-(2-benzyl-3-phenyl-propionyloxy)-4-oxo-pentanoic acid as a white solid, mp 156-168°C, dec.

Analysis calculated for $C_{42}H_{50}N_4O_{12} \cdot H_2O$ (820.902):

C, 61.45; H, 6.38; N, 6.82.

Found: C, 61.43; H, 6.27; N, 6.76.

EXAMPLE 6i

5-(2-Benzyl-3-phenyl-propionyloxy)-3-{2-[4-carboxy-2-(3-phenyl-propionylamino)-butyrylamino]-3-methyl-butyrylamino}-4-oxo-pentanoic acid as a white solid.

Analysis calculated for $C_{40}H_{47}N_3O_{10} \cdot 0.13\ CF_3CO_2H$ (744.658):

C, 64.94; H, 6.38; N, 5.64.

Found: C, 64.93; H, 6.63; N, 5.61.

EXAMPLE 6j

3-{2-[4-Carboxy-2-(3-phenyl-propionylamino)-butyrylamino]-3-methyl-butyrylamino}-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid as a white solid.

Analysis calculated for $C_{36}H_{41}N_3O_{10}$•0.44 CF_3CO_2H (725.913):

C, 61.02; H, 5.75; N, 5.79.

Found: C, 61.04; H, 6.04; N, 6.19.

EXAMPLE 6k

3-(2-Benzyloxycarbonylamino-3-methyl-butyrylamino)-5-(3,3-diphenyl-propionyloxy)-4-oxo-pentanoic acid

MS (APCI) m/z 588.9 (M+1)

EXAMPLE 6l

3-(2-Acetylamino-3-hydroxy-butyrylamino)-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid

MS (APCI) m/z 456.9 (M-1)

EXAMPLE 6m

3-(2-Acetylamino-3-hydroxy-butyrylamino)-5-(3,3-diphenyl-propionyloxy)-4-oxo-pentanoic acid

MS (APCI) m/z 496.9 (M-1)

EXAMPLE 6n

3-(2-{2-[2-Acetylamino-3-(1H-indol-3-yl)-propionylamino]-4-carboxy-butyrylamino}-3-methyl-butyrylamino)-5-(2-benzyl-3-phenyl-propionyloxy)-4-oxo-pentanoic acid as an orange solid.

Analysis calculated for $C_{44}H_{51}N_5O_{11}$•1.33 H_2O (849.944):

C, 62.18; H, 6.36; N, 8.24.

Found: C, 62.16; H, 6.24; N, 8.18.

EXAMPLE 6o

5-(3,3-Diphenyl-propionyloxy)-4-oxo-3-[2-(4-phenyl-butyrylamino)-propionylamino]-pentanoic acid

MS (APCI) m/z 573.2 (M+1)

EXAMPLE 7

3-(2-{2-[2-Acetylamino-3-(1H-indol-3-yl)-propionylamino]-4-carboxy-butyrylamino}-3-methyl-butyrylamino)-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid

Step A

A solution of 3-[2-(2-benzyloxycarbonylamino-4-tert-butoxycarbonyl-butyrylamino)-3-methyl-butyrylamino]-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid tert-butyl ester (5.3 g, 6.7 mmol, Example 6, Step F) in 300 mL of ethanol:THF (2:1) was treated with 0.6 g of 20% Pd/C and hydrogenated at room temperature, balloon pressure for 3 hours. The sample was filtered and concentrated to 5.0 g (>100%) of 3-[2-(2-amino-4-tert-butoxycarbonyl-butyrylamino)-3-methyl-butyrylamino]-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid tert-butyl ester as yellow oil.

Step B

A mixture of 3-[2-(2-amino-4-tert-butoxycarbonyl-butyrylamino)-3-methyl-butyrylamino]-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid tert-butyl ester (1.25 g, 1.91 mmol, Example 7, Step A), AcTrp-OH (0.52 g, 2.10 mmol), HOBT•H_2O (0.32 g, 2.10 mmol), EDCI•HCl (0.40 g, 2.10 mmol) and 4-methylmorpholine (0.26 mL, 2.36 mmol) in 25 mL of dichloromethane was stirred at room temperature for 12 hours. The sample was concentrated, then partitioned between ethyl acetate and sat. $NaHCO_3$ solution. The organic extract was washed with sat. KH_2PO_4 and brine solutions, dried ($MgSO_4$), filtered and concentrated. The residue was chromatographed (MPLC, silica gel, 25% hexanes-75% ethyl acetate) to give 0.95 g (56%) of 3-(2-{2-[2-acetylamino-3-(1H-indol-3-yl)-propionylamino]-4-tert-butoxycarbonyl-butyrylamino}-3-methyl-

butyrylamino)-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid, tert-butyl ester as a white solid.

Step C

A solution of 3-(2-{2-[2-acetylamino-3-(1H-indol-3-yl)-propionylamino]-4-tert-butoxycarbonyl-butyrylamino}-3-methyl-butyrylamino)-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid, tert-butyl ester (0.93 g, 1.05 mmol, Example 7, Step B) and 10 mL of trifluoroacetic acid in 20 mL of dichloromethane was stirred at room temperature for 2 hours. The sample was concentrated to a purple oil. Ether (~50 mL) was added and the oil slowly solidified. The sample was filtered and vacuum dried to give 0.78 g (96%) of 3-(2-{2-[2-acetylamino-3-(1H-indol-3-yl)-propionylamino]-4-carboxy-butyrylamino}-3-methyl-butyrylamino)-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid as a light purple solid.

Analysis calculated for $C_{40}H_{45}N_5O_{11}\cdot 0.50\ H_2O$ (780.839):

C, 61.53; H, 5.94; N, 8.97.

Found: C, 61.45; H, 6.12; N, 8.81.

In a process analogous to Example 7, the corresponding compounds were prepared:

EXAMPLE 7a

3-[2-(2-Acetylamino-4-carboxy-butyrylamino)-3-methyl-butyrylamino]-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid as an off-white solid.

Analysis calculated for $C_{29}H_{35}N_3O_{10}\cdot H_2O$ (603.632):

C, 57.70; H, 6.18; N, 6.96.

Found: C, 57.59; H, 6.11; N, 7.28.

EXAMPLE 7b

3-(2-{2-[2-Acetylamino-3-(4-hydroxy-phenyl)-propionylamino]-4-carboxy-butyrylamino}-3-methyl-butyrylamino)-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid as a white solid.

Analysis calculated for $C_{38}H_{44}N_4O_{12}\cdot H_2O$ (766.809):

C, 59.52; H, 6.00; N, 7.31.

Found: C, 59.36. H, 5.79; N, 7.24.

EXAMPLE 8

3-[(2-Carboxy-cyclohexanecarbonyl)-amino]-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid

Step A

A solution of the hydrochloride salt of 3 amino-5-(naphthalene-1-yl-acetoxy)-4-oxo-pentanoic acid tert-butyl ester (1.7 g, 4.6 mmol) (Example 2, Step A) and 1,2-trans-cyclohexanedicarboxylic anhydride (0.79 g, 5.1 mmol) in 30 mL of methylene chloride was treated with pyridine (5 mL) and a catalytic amount of dimethylaminopyridine (DMAP). The reaction mixture was stirred at room temperature overnight and the solvent was evaporated. The residue was partitioned between diethyl ether and 5% HCl, and the layers separated. The organic layer was washed with 5% HCl, dried ($MgSO_4$), filtered, and concentrated. The crude product was purified by flash chromatography (silica gel , 15% acetone/1% formic acid/methylene chloride) to give 0.3 g of pure 3-[(2-carboxy-cyclohexanecarbonyl)-amino]-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid tert-butyl ester as a mixture of two diastereomers.

MS (APCI) m/z 524 (M-1).

Step B

A solution of 3-[(2-carboxy-cyclohexanecarbonyl)-amino]-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid tert-butyl ester (0.181 g, 0.3444 mmol) in 6 mL methylene chloride was treated with 4 mL of 50% trifluoroacetic acid (in methylene chloride). The reaction mixture was stirred at room temperature for 4 hours, diluted with toluene (50 mL), and concentrated under reduced pressure to give 3-[(2-carboxy-cyclohexanecarbonyl)-amino]-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid as a colorless solid (mixture of two diastereomers).

MS (APCI m/z 470 (M+1)

EXAMPLE 8a

3-[(2-Methoxycarbonyl-cyclohexanecarbonyl)-amino]-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid

Step A

A solution of 3-[(2-carboxy-cyclohexanecarbonyl)-amino]-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid tert-butyl ester (2.3 mmol) (Example 8, Step A) in 5 mL methylene chloride was treated with excess of diazomethane in ether. The reaction mixture was stirred for 3 hours at room temperature and then quenched by the dropwise addition of glacial acetic. The solvent was evaporated under reduced pressure to give 3-[(2-methoxycarbonyl-cyclohexanecarbonyl)-amino]-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid tert-butyl ester.
MS (APCI) m/z 540 (M+1)

Step B

The targeted compound was prepared from the corresponding tert-butyl ester as described for Example 8, Step B to yield 3-[(2-methoxycarbonyl-cyclohexanecarbonyl)-amino]-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid.
MS (APCI) m/z 484 (M+1)

EXAMPLE 8b

3-[(2-Carbamoyl-cyclohexanecarbonyl)-amino]-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid

Step A

A solution of DCC (0.18 g, 0.88 mmol) and HOBT (0.12 g, 0.88 mmol) in 20 mL methylene chloride was added dropwise to a solution of 3-[(2-carboxy-cyclohexanecarbonyl)-amino]-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid tert-butyl ester (0.45 g, 0.85 mmol) (from Example 2, Step A) and triethylamine (0.099 g, 0.98 mmol) in 25 mL methylene chloride and the reaction mixture was stirred for 30 minutes at room temperature. Hexamethyldisilazane (0.80 g, 4.9 mmol) was added, and the reaction mixture was stirred at room temperature overnight. The reaction mixture was poured into 100 mL ether and extracted three times with 5% HCl, then washed with saturated NaCl. The organic layer was dried

($MgSO_4$), filtered and concentrated under reduced pressure. The residue was taken up in ether/hexane, filtered, and concentrated to give a sticky foam. After purification by flash chromatography, 3[(2-carbamoyl-cyclohexanecarbonyl)-amino]-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid tert-butyl ester (0.086 g) was obtained as a mixture of two diastereomers.

MS (APCI) m/z 525 (M+1)

Step B

The targeted compound was prepared from the corresponding tert-butyl ester as described for Example 8, Step B to yield 3-[(2-carbamoyl-cyclohexanecarbonyl)-amino]-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid.

MS (APCI) m/z 467 (M-1).

EXAMPLE 9

3-(3-Benzylsulfanyl-2-methyl-propionylamino)-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid

Step A

To a solution of 3-benzylsulfanyl-2-methyl-propionic acid (3.3 g, 15.8 mmol) and H-Asp(OtBu)OMe•HCl (3.7 g, 15.8 mmol) in dimethylformamide (50 mL) was added at 0°C 1-ethyl-3-(3′-dimethylaminopropyl)carbodiimide•HCl (3.25 g, 17.0 mmol) and triethylamine (4.4 g, 43.8 mmol). The mixture was stirred at room temperature for 16 hours. Most of the solvent was removed under reduced pressure, the residue was partitioned between ethyl acetate and 5% citric acid. The ethyl acetate extract was washed with sodium hydrogen carbonate and water, dried over sodium sulfate, and concentrated to give 6.3 g of an amorphous residue. The residue was dissolved in 100 mL of dioxane/water (1:1) and hydrolyzed in the presence of thymolphthalein by dropwise addition of 1N NaOH (15.0 mL). After evaporation of most of the dioxane and dilution with water, the aqueous solution was extracted with ether, acidified with dilute HCl to pH 2-3, and the product extracted into ethyl acetate. The ethyl acetate extract was washed with water, dried over sodium sulfate, and concentrated to give 6.3 g of crude product.

Chromatography over silica gel (dichloromethane/methanol 30:1) afforded 5.5 g of N-(3-benzylsulfanyl-2-methyl-propionyl)-aspartic acid 4-tert-butyl ester.

Step B

To a solution of N-(3-benzylsulfanyl-2-methyl-propionyl)-aspartic acid 4-tert-butyl ester (5.4 g, 14.2 mmol) in tetrahydrofuran (670 mL) at -15°C was added N-methylmorpholine (1.5 mL, 16.0 mmol) followed by dropwise addition of ethyl chloroformate (1.6 mL, 16.0 mmol). After 15 minutes at -10°C, 110 mL of a 0.2N solution of diazomethane in ether was added dropwise. The reaction was kept for 2 hours at room temperature, then 40 mL of a solution of 48% HBr in glacial acetic acid (1:1) was added dropwise at 0°C. After stirring for 15 minutes, the reaction mixture was poured into ethyl acetate. The organic phase was washed 3× with saturated aqueous sodium hydrogencarbonate then with water, dried over sodium sulfate, and concentrated under reduced pressure to give 3-(3-benzylsulfanyl-2-methyl-propion-1-yl)amino-5-bromo-4-oxo-pentanoic acid tert-butyl ester (4.2 g).

Step C

To a mixture of 3-(3-benzylsulfanyl-2-methyl-propionyl)amino-5-bromo-4-oxo-pentanoic acid tert-butyl ester (0.92 g, 2.0 mmol) and potassium fluoride (0.35 g, 6.0 mmol) in dimethylformamide (40 mL) was added 1-naphthalenelacetic acid (0.37 g, 2.0 mmol). The mixture was stirred at room temperature for 16 hours. Most of the solvent was evaporated under reduced pressure, the residue was partitioned between ethyl acetate and water. The organic phase was washed successively with aqueous sodium hydrogen carbonate and water, dried over sodium sulfate, and evaporated under reduced pressure. Chromatography over silica (dichloromethane/acetone 40:1) gave 0.46 g 3-(3-benzylsulfanyl-2-methyl-propionyl)amino-5-(naphthalene-1-yl-acetoxy)-4-oxo-pentanoic acid tert-butyl ester.

Step D

3-(3-Benzylsulfanyl-2-methyl-propionyl)amino-5-(naphthalene-1-yl)acetoxy-4-oxo-pentanoic acid tert-butyl ester (0.12 g, 0.21 mmol) in 10 mL of a 1:1 mixture of dichloromethane/trifluoroacetic acid containing 0.1 mL of anisol was stirred at room temperature for 45 minutes. Evaporation under reduced pressure followed by chromatography over silica (dichloromethane/methanol 40:1 to 20:1) gave 3-(3-benzylsulfanyl-2-methyl-propionylamino)-5-(naphthalene-1-yl-acetoxy)-4-oxo-pentanoic acid (0.11 g).

MS (ESI) m/z 508.4 (M+1)

EXAMPLE 9a

3-(2-Methyl-3-phenylmethanesulfonyl-propionylamino)-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid

Step A

To 3-(3-phenylmethanesulfanyl-2-methyl-propionylamino)-5-(naphthalene-1-yl-acetoxy)-4-oxo-pentanoic acid tert-butyl ester (0.33 g, 0.58 mmol) in ethanol (10 mL) from Example 9, Step C in 10 mL of ethanol was added at 0°C under stirring potassium monoperoxysulfate (1.74 mmol as a solution of 0.54 g oxone in 2 mL of water). The resulting slurry was stirred for 4 hours at room temperature. The reaction mixture was partitioned between dichloromethane and water. The organic phase was washed with aqueous sodium hydrogen carbonate and water, dried over sodium sulfate, and evaporated under reduced pressure. Chromatography over silica (dichloromethane/acetone 40:1) gave 0.25 g of 3-(3-phenylmethanesulfanyl-2-methyl-propionyl)amino-5-(naphthalene-1-yl-acetoxy)-4-oxo-pentanoic acid tert-butyl ester.

Step B

3-(3-Phenylmethanesulfanyl-2-methyl-propionyl)amino-5-(naphthalene-1-yl-acetoxy)-4-oxo-pentanoic acid tert-butyl ester (0.21g, 0.35 mmol) in 20 mL of a 1:1 mixture of dichloromethane/trifluoroacetic acid containing 0.2 mL of anisol was stirred at room temperature for 45 minutes. Evaporation under reduced pressure followed crystallization from dichloromethane/ether/hexane gave

3-(2-methyl-3-phenylmethanesulfonyl-propionylamino)-5-(naphthalene-1-yl-acetoxy)-4-oxo-pentanoic acid (0.16 g).

MS (ESI) m/z 540.2 (M+1)

EXAMPLE 9b

3-[3-(2-Carboxy-ethanesulfanyl)-2-methyl-propionylamino]-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid

Step A

To a solution of 3-(2-tert-butyloxycarbonyl)ethanesulfanyl-2-methyl-propionic acid (5.0 g, 20.0 mmol) and H-Asp(OtBu)OMe•HCl (4.8 g, 20.0 mmol) in dimethylformamide (60 mL) was added at 0°C 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide•HCl (3.85 g, 20.0 mmol) and triethylamine (6.0 g, 60 mmol). The mixture was stirred at room temperature for 16 hours. Most of the solvent was removed under reduced pressure, the residue was partitioned between ethyl acetate and 5% citric acid. The ethyl acetate extract was washed with sodium hydrogen carbonate and water, dried over sodium sulfate, and concentrated to give after silica gel chromatography (dichloromethane/acetone 15:1) 5.5 g of an amorphous residue. The residue was dissolved in 50 mL of dioxane/water (4:1) and hydrolyzed in the presence of thymolphthalein by dropwise addition of 1N NaOH (12.5 mL). After evaporation of most of the dioxane and dilution with water, the aqueous solution was extracted with ether, acidified with dilute HCl to pH 2-3, and the product extracted into ethyl acetate. The ethyl acetate extract was washed with water, dried over sodium sulfate, and concentrated to give 5.2 g of N-(3-(2-tert-butyloxycarbonyl)ethanesulfanyl-2-methyl-propionyl))-aspartic acid 4-tert-butyl ester.

Step B

To a solution of N-(3-(2-tert-butyloxycarbonyl)ethanesulfanyl-2-methyl-propionyl)-aspartic acid 4-tert-butyl ester (4.5 g, 10.7 mmol) in tetrahydrofuran (60 mL) at -15°C was added N-methylmorpholine (1.65 mL, 15.0 mmol) followed by dropwise addition of ethyl chloroformate (1.35 mL, 13.5 mmol). After 15 minutes at -10°C, 105 mL of a ca 0.2N solution of diazomethane in ether was

added dropwise. The reaction was kept for 2 hours at room temperature, then 30 mL of a solution of 48% HBr in glacial acetic acid (1:1) was added dropwise at 0°C. After stirring for 15 minutes, the reaction mixture was poured into ethyl acetate. The organic phase was washed 3× with saturated aqueous sodium hydrogencarbonate then with water, dried over sodium sulfate, and concentrated under reduced pressure to give 3-(3-(2-tert-butyloxycarbonyl)ethanesulfanyl-2-methyl-propion-1-yl)amino-5-bromo-4-oxo-pentanoic acid tert-butyl ester (4.2 g).

Step C

To a mixture of 3-(3-(2-tert-butyloxycarbonyl)ethanesulfanyl-2-methyl-propionyl)amino-5-bromo-4-oxo-pentanoic acid tert-butyl ester (1.65 g, 3.3 mmol) and potassium fluoride (0.58 g, 10.0 mmol) in dimethylformamide (50 mL) was added 1-naphthalenelacetic acid (0.75 g, 4.0 mmol). The mixture was stirred at room temperature for 16 hours. Most of the solvent was evaporated under reduced pressure, the residue was partitioned between ethyl acetate and water. The organic phase was washed with aqueous sodium hydrogen carbonate and water, dried over sodium sulfate, and evaporated under reduced pressure. Chromatography over silica (dichloromethane/acetone 40:1) gave 0.89 g 3-(3-(2-tert-butyloxycarbonyl)-ethanesulfanyl-2-methyl-propionyl)amino-5-(naphthalene-1-yl-acetoxy)-4-oxo-pentanoic acid tert-butyl ester.

Step D

3-(3-(2-tert-Butyloxycarbonyl)ethanesulfanyl-2-methyl-propionyl)amino-5-(naphthalene-1-yl)acetoxy-4-oxo-pentanoic acid tert-butyl ester (0.21 g, 0.33 mmol) in 10 mL of a 1:1 mixture of dichloromethane/trifluoroacetic acid containing 0.1 mL of anisol was stirred at room temperature for 45 minutes. Evaporation under reduced pressure and treatment of the residue with dichloromethane/ether/hexane gave 0.08 g of 3-[(3-(2-carbethoxy-ethanesulfanyl)-2-methyl-propionylamino]-5-(naphthalene-1-yl-acetoxy)-4-oxo-pentanoic acid (0.11 g).

MS (ESI) m/z 490.3 (M+1)

EXAMPLE 9c

5-(2-Benzyl-3-phenyl-propionyloxy)-3-[3-(2-carboxy-ethanesulfonyl)-2-methyl-propionylamino]-4-oxo-pentanoic acid

Step A

To 5-(2-benzyl-3-phenyl-propionyloxy)-3-[3-(2-carboxy-ethanesulfanyl)-2-methyl-propionylamino]-4-oxo-pentanoic acid, tert-butyl ester (0.59 g, 0.9 mmol) prepared as described in Example 3 in 15 mL of ethanol was added at 0°C under stirring potassium monoperoxysulfate (2.8 mmol as a solution of 0.86 g Oxone in 3 mL of water). The resulting slurry was stirred for 3 hours at room temperature. The reaction mixture was partitioned between dichloromethane and water. The organic phase was washed with aqueous sodium hydrogen carbonate and water, dried over sodium sulfate, and evaporated under reduced pressure. Chromatography over silica (dichloromethane/acetone 30:1) gave 0.39 g of 5-(2-benzyl-3-phenyl-propionyloxy)-3-[3-(2-carboxy-ethanesulfonyl)-2-methyl-propionylamino]-4-oxo-pentanoic acid, tert-butyl ester.

Step B

5-(2-Benzyl-3-phenyl-propionyloxy)-3-[3-(2-carboxy-ethanesulfonyl)-2-methyl-propionylamino]-4-oxo-pentanoic acid, tert-butyl ester (0.33g, 0.48 mmol) in 20 mL of a 1:1 mixture of dichloromethane/trifluoroacetic acid containing 0.1 mL of anisol was stirred at room temperature for 45 minutes. Evaporation under reduced pressure followed crystallization from ether/hexane gave 5-(2-benzyl-3-phenyl-propionyloxy)-3-[3-(2-carboxy-ethanesulfonyl)-2-methyl-propionylamino]-4-oxo-pentanoic acid, tert-butyl ester (0.12 g).

MS (ESI) m/z 576.3 (M+1)

EXAMPLE 9d

5-(2-Benzyl-3-phenyl-propionyloxy)-3-[3-(3-carboxy-propane-1-sulfinyl)-2-methyl-propionylamino]-4-oxo-pentanoic acid

Step A

To 5-(2-benzyl-3-phenyl-propionyloxy)-3-[3-(3-carboxy-propanesulfanyl)-2-methyl-propionylamino]-4-oxo-pentanoic acid, tert-butyl ester (0.28 g,

0.42 mmol) prepared as described in Example 3 in 4 mL of dichloromethane was added at -50°C under stirring 0.13 of 70% 3-chloroperbenzoic acid (0.53 mmol). The reaction mixture kept for 1 hour at -30°C then partitioned between dichloromethane and water. The organic phase was washed with aqueous sodium hydrogen carbonate (2×) and water, dried over sodium sulfate, and evaporated under reduced pressure. Chromatography over silica (dichloromethane/acetone 10:1) gave 0.15 g of 5-(2-benzyl-3-phenyl-propionyloxy)-3-[3-(3-carboxy-propane-1-sulfinyl)-2-methyl-propionylamino]-4-oxo-pentanoic acid, tert-butyl ester.

Step B

5-(2-Benzyl-3-phenyl-propionyloxy)-3-[3-(3-carboxy-propane-1-sulfinyl)-2-methyl-propionylamino]-4-oxo-pentanoic acid, tert-butyl ester (0.40 g, 0.57 mmol) in 30 mL of a 1:1 mixture of dichloromethane/trifluoroacetic acid containing 0.1 mL of anisol was stirred at room temperature for 45 minutes. Evaporation under reduced pressure followed crystallization from ether/hexane gave the title compound (0.14 g).

MS (ESI) m/z 574.3 (M+1)

In a process analogous to Example 9, using appropriately substituted sulfanyl carboxylic acids, the corresponding compounds were prepared:

EXAMPLE 9e

5-(Naphthalen-1-yl-acetoxy)-4-oxo-3-(2-phenylmethanesulfanyl-propionylamino)-pentanoic acid

MS (ESI) m/z 494.3 (M+1)

EXAMPLE 9f

3-(2-Methyl-3-phenylsulfanyl-propionylamino)-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid

MS (EI) m/z 493 (M+)

EXAMPLE 9g

5-(2-Benzyl-3-phenyl-propionyloxy)-3-(2-methyl-3-phenylsulfanyl-propionylamino)-4-oxo-pentanoic acid

MS (ESI) m/z 548.3 (M+1)

EXAMPLE 9h

3-(2-Methyl-3-phenethylsulfanyl-propionylamino)-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid

MS (ESI) m/z 522.2 (M+1)

EXAMPLE 9i

5-(2-Benzyl-3-phenyl-propionyloxy)-3-(2-methyl-3-phenethylsulfanyl-propionylamino)-4-oxo-pentanoic acid

MS (ESI) m/z 576.3 (M+1)

EXAMPLE 9j

5-(2-Benzyl-3-phenyl-propionyloxy)-3-(3-benzylsulfanyl-2-methyl-propionylamino)-4-oxo-pentanoic acid

MS (ESI) m/z 562.3 (M+1)

EXAMPLE 9k

5-(2-Benzyl-3-phenyl-propionyloxy)-3-(2-benzylsulfanyl-propionylamino)-4-oxo-pentanoic acid

MS (ESI) m/z 546.3 (M+1)

EXAMPLE 9l

3-[2-Methyl-3-(3-phenyl-propylsulfanyl)-propionylamino]-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid

MS (ESI) m/z 536.4 (M+1)

In a process analogous to Example 9a, using appropriately substituted sulfone carboxylic acids, the corresponding compounds were prepared:

EXAMPLE 9m

3-(3-Benzenesulfonyl-2-methyl-propionylamino)-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid

(ESI) MS m/z 526.4 (M+1)

EXAMPLE 9n

3-(3-Benzenesulfonyl-2-methyl-propionylamino)-5-(2-benzyl-3-phenyl-propionyloxy)-4-oxo-pentanoic acid

MS (ESI) m/z 580.2 (M+1)

EXAMPLE 9o

5-(2-Benzyl-3-phenyl-propionyloxy)-3-[2-methyl-3-(2-phenyl-ethanesulfonyl)-propionylamino]-4-oxo-pentanoic acid

MS (ESI) m/z 608.2 (M+1)

EXAMPLE 9p

3-[2-Methyl-3-(2-phenyl-ethanesulfonyl)-propionylamino]-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid

MS (ESI) m/z 554.2 (M+1)

EXAMPLE 9q

5-(Naphthalen-1-yl-acetoxy)-4-oxo-3-(2-phenylmethanesulfonyl-propionylamino)-pentanoic acid

MS (ESI) m/z 526.2 (M+1)

EXAMPLE 9r

5-(2-Benzyl-3-phenyl-propionyloxy)-3-(2-methyl-3-phenylmethanesulfonyl-propionylamino)-4-oxo-pentanoic acid

MS (ESI) m/z 594.2 (M+1)

EXAMPLE 9s

5-(2-Benzyl-3-phenyl-propionyloxy)-4-oxo-3-(2-phenylmethanesulfonyl-propionylamino)-pentanoic acid

MS (ESI) m/z 580.1 (M+1)

EXAMPLE 9t

3-[2-Methyl-3-(3-phenyl-propane-1-sulfonyl)-propionylamino]-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid

MS (ESI) m/z 568.2 (M+1)

EXAMPLE 9u

5-(2-Benzyl-3-phenyl-propionyloxy)-3-[2-methyl-3-(3-phenyl-propane-1-sulfonyl)-propionylamino]-4-oxo-pentanoic acid

MS (ESI) m/z 622.3 (M+1)

In a process analogous to Example 9b, using appropriately substituted sulfanyl carboxylic acids, the corresponding compounds were prepared:

EXAMPLE 9v

5-(2-Benzyl-3-phenyl-propionyloxy)-3-[3-(2-carboxy-ethylsulfanyl)-2-methyl-propionylamino]-4-oxo-pentanoic acid

MS (ESI) m/z 544.4 (M+1)

EXAMPLE 9w

3-[3-(3-Carboxy-propylsulfanyl)-2-methyl-propionylamino]-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid

MS (ESI) m/z 504.2 (M+1)

EXAMPLE 9x

5-(2-Benzyl-3-phenyl-propionyloxy)-3-[3-(3-carboxy-propylsulfanyl)-2-methyl-propionylamino]-4-oxo-pentanoic acid

MS (ESI) m/z 558.2 (M+1)

EXAMPLE 9y

3-(3-Carboxymethylsulfanyl-2-methyl-propionylamino)-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid

MS (ESI) m/z 476.1 (M+1)

EXAMPLE 9z

5-(2-Benzyl-3-phenyl-propionyloxy)-3-(3-carboxymethylsulfanyl-2-methyl-propionylamino)-4-oxo-pentanoic acid

MS (ESI) m/z 530.1 (M+1)

In a process analogous to Example 9c, using appropriately substituted sulfonyl carboxylic acids, the corresponding compounds were prepared:

EXAMPLE 9aa

3-[3-(2-Carboxy-ethanesulfonyl)-2-methyl-propionylamino]-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid

MS (ESI) m/z 522.3 (M+1)

EXAMPLE 9bb

3-[3-(3-Carboxy-propane-1-sulfonyl)-2-methyl-propionylamino]-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid

MS (ESI) m/z 536.3 (M+1)

EXAMPLE 9cc

3-(3-Carboxymethanesulfonyl-2-methyl-propionylamino)-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid

MS (ESI) m/z 508.3 (M+1)

EXAMPLE 9dd

5-(2-Benzyl-3-phenyl-propionyloxy)-3-[3-(3-carboxy-propane-1-sulfonyl)-2-methyl-propionylamino]-4-oxo-pentanoic acid

MS (ESI) m/z 588.3 (M-H)

EXAMPLE 9ee

5-(2-Benzyl-3-phenyl-propionyloxy)-3-(3-carboxymethanesulfonyl-2-methyl-propionylamino)-4-oxo-pentanoic acid

MS (ESI) m/z 560.2 (M-H)

In a process analogous to Example 9d, using appropriately substituted sulfinyl carboxylic acids, the corresponding compounds were prepared:

EXAMPLE 9ff

3-[3-(3-Carboxy-propane-1-sulfinyl)-2-methyl-propionylamino]-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid

MS (ESI) m/z 520.4 (M+1)

EXAMPLE 9gg

3-[2-Methyl-3-(3-phenyl-propane-1-sulfinyl)-propionylamino]-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid

MS (ESI) m/z 552.2 (M+1)

EXAMPLE 9hh

5-(2-Benzyl-3-phenyl-propionyloxy)-3-[2-methyl-3-(3-phenyl-propane-1-sulfinyl)-propionylamino]-4-oxo-pentanoic acid

MS (ESI) m/z 606.3 (M+1)

EXAMPLE 10

3-(2-Carbamoylmethyl-3-methyl-butyrylamino)-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid

Step A

A solution of (4S)-(-)-4-isopropyl-2-oxazolidinone (19.85 g, 0.154 mol) in 400 mL of THF at -78°C under N_2 was treated dropwise with *n*-butyl lithium (64.5 mL, 0.161 mol, 2.5 M solution in hexanes). Solid formed. The mixture was stirred at -78°C for 30 minutes, then treated with dropwise addition of *iso*-valeryl

chloride (20.6 mL, 0.169 mol). The reaction was allowed to warm to room temperature slowly overnight. The sample was concentrated then partitioned between EtOAc and saturated KH_2O_4solution. The organic extract was washed with brine, dried ($MgSO_4$, and the resultant yellow oil was chromatographed (MPLC, silica gel, 10% EtOAc in hexanes) to give 29.8 g (91%) of N-acyloxazolidone as a light yellow oil.

Step B

A solution of N-acyloxazolidone (20.8 g, 97.5 mmol, Example 10, Step A) in 500 mL of THF at -78°C under N_2 was treated dropwise with sodium bis(trimethylsilyl)amide (107 mL, 107 mmol, 1.0 M solution in THF). The solution was stirred at -78°C for 30 minutes, then treated dropwise with a solution of *tert*-butyl bromoacetate (18.0 mL, 121.9 mmol) in 100 mL of THF. The sample was stirred at -78°C for 1 hour, then quenched by dropwise addition of saturated KH_2PO_4 solution (~125 mL). The mixture was warmed to room temperature, concentrated (to remove most of the THF), then extracted with ether. The organic extract was washed with saturated $NaHCO_3$ and brine solutions, dried ($MgSO_4$), concentrated and crystallized from ether-pet ether to give 21.1 g (66%) of [(S-(R*,R*)]-3-(4-isopropyl-2-oxo-oxazolidine-3-carbonyl)-4-methyl-pentanoic acid, tert-butyl ester, as a white solid.

Analysis calculated for $C_{17}H_{29}NO_5$ (327.424):

C, 62.36; H, 8.93; N, 4.28.

Found: C, 62.30; H, 9.07; N, 4.09.

Step C

The hydrolysis of the N-acyloxazolidone was achieved using lithium hydroperoxide following the procedure of Evans D.A., et al., Tet. Lett., 1987;28:6141-6144. To a stirring solution at 0°C of [(S-(R*,R*)]-3-(4-isopropyl-2-oxo-oxazolidine-3-carbonyl)-4-methyl-pentanoic acid, tert-butyl ester (9.05 g, 27.64 mmol, Example 10, Step B) in 250 mL of THF was added dropwise hydrogen peroxide (14.1 mL, 138 mmol, 30 wt% solution in water) followed by

1.0 M lithium hydroxide solution (55.3 mL, 55.3 mmol). The reaction was allowed to warm to room temperature slowly overnight. The reaction was concentrated (to remove most of the THF), then the basic solution was washed with CH_2Cl_2 (2 × 100 mL). The aqueous phase was cooled, acidified with saturated KH_2PO_4 solution to a pH ~5 and extracted into EtOAc. The organic extract was washed with brine solution, dried ($MgSO_4$), and concentrated to give 5.66 g (95%) of (S)-2-isopropyl succinic acid 4–tert-butyl ester as a colorless oil, which was used without further purification.

Step D

A mixture of (S)-2-isopropyl succinic acid 4–tert-butyl ester (10.77 g, 49.80 mmol), (S)-2-amino-succinic acid 1-allyl ester 4-benzyl ester hydrochloride (14.93 g, 49.81 mmol), HOBT•H_2O (8.4 g, 54.8 mmol), EDCI•HCl (10.5 g, 54.8 mmol), and 4-methylmorpholine (8.2 mL, 74.6 mmol) in 250 mL of CH_2Cl_2 was stirred at room temperature for 12 hours. The mixture was concentrated, then partitioned between EtOAc and saturated $NaHCO_3$ solution. The EtOAc extract was washed with saturated KH_2PO_4 and brine solutions, dried ($MgSO_4$), filtered, concentrated, and chromatographed (MPLC, silica gel, 20% EtOAc in hexanes) to give 19.21 g (84%) of [S-(R*,R*)]-2-(2-tert-butoxycarbonylmethyl-3-methyl-butyrylamino)-succinic acid 1-allyl ester 4-benzyl ester as light yellow oil.

Step E

A solution of [S-(R*,R*)]-2-(2-tert-butoxycarbonylmethyl-3-methyl-butyrylamino)-succinic acid 1-allyl ester 4-benzyl ester (9.3 g, 23.0 mmol, Example 10, Step D) and trifluoroacetic acid (35 mL) in 35 mL of CH_2Cl_2 was stirred at room temperature under N_2 for 2 hours. The sample was concentrated, redissolved into CH_2Cl_2, then treated with EDCI•HCl (8.8 g, 46.0 mmol), HOBT•H_2O (6.2 g, 46.0 mmol), and O-benzylhydroxylamine hydrochloride (7.3 g, 46.0 mmol). 4-Methylmorpholine (11.6 g, 115 mmol) was added dropwise, and the reaction mixture was stirred at room temperature overnight. The sample

was diluted with $CH2Cl_2$ and washed successively with 5% HCl and sat. $nacho_3$ solutions. The organic extract was dried (Na_2SO_4) and concentrated to afford 10.25 g (88%) of the O-benzyl hydroxamate as a white solid which was carried on to the next step without further purification.

Step F

The allyl ester was cleaved employing the procedure of Dessolin M., et al., Tet. Lett., 1995;36:5741-5744. A solution at 0°C under N_2 of allyl ester (10.25 g, 19.7 mmol, Example 10, Step E) and tetrakis(triphenylphosphine)palladium (0) (0.462 g, 0.40 mmol) in CH_2Cl_2 was treated dropwise with phenylsilane (4.26 g, 39.4 mmol). The reaction mixture was allowed to warm to room temperature over a period of 1 hour, then washed with saturated KH_2PO_4 solution. The organic layer was extracted with 0.5N NaOH. The basic aqueous phase was acidified with concentrated HCl and extracted with EtOAc. The organic extract was dried (Na_2SO_4), filtered, and concentrated to afford 6.2 g (72%) of the substituted succinic acid 4-benzyl ester as foamy white solid.

To a solution of above acid (6.0 g, 12.8 mmol) and 4-methylmorpholine (1.3 g, 12.8 mmol) in THF (50 mL) at -42°C was added isobutyl chloroformate (1.8 g, 12.8 mmol) dropwise. After stirring 30 minutes, the reaction mixture was added to a solution of diazomethane in diethyl ether (~0.5 M, 200 mL) at 0°C. The reaction mixture was stirred for 2 hours at room temperature then cooled to 0°C. A solution of 48% HBr (20 mL) and HOAc (20 mL) was added dropwise, and the reaction was stirred for 30 minutes at 0°C. The sample was diluted with diethyl ether and washed with water (2×) and saturated $NaHCO_3$ solution (2×). The organic layer was dried (Na_2SO_4) and concentrated. The residue was dissolved in CH_2Cl_2, and the product was precipitated with hexanes. The solid was collected by filtration, washed well with hexanes, and dried to afford 1.5 g (15%) of the bromomethyl ketone as a white solid.

A mixture of the bromomethyl ketone (0.440 g, 0.82 mmol), 1-naphthylacetic acid (0.300 g, 1.61 mmol), and potassium fluoride (0.116 g,

2.0 mmol) in 2.0 mL of DMF was stirred at room temperature for 12 hours. The reaction mixture was diluted with EtOAc and washed successively with water (2×) and saturated $NaHCO_3$ solution. The organic layer was dried (Na_2SO_4) and concentrated. The residue was crystallized from CH_2Cl_2-hexanes to afford 0.430 g (80%) of napthyl acetic acid ester methyl ketone as a white solid.

Step G

To a solution of substituted succinic acid 4-benzyl ester (0.43 g, Example 10, Step F) in 75 mL of THF was treated with Pd/C (0.050 g), and the mixture was hydrogenated at 50 psi H_2, room temperature for 2 hours. The reaction mixture was filtered and Raney Nickel (0.10 g) was added. The reaction mixture was again hydrogenated at 50 psi for 17 hours. The sample was filtered. The filtrate was concentrated, and the residue was crystallized from acetone-hexanes to afford 0.111 g (45%) of 3-(2-carbamoylmethyl-3-methyl-butyrylamino)-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid as a white solid.

Analysis calculated for $C_{24}H_{28}N_2O_7 \cdot 0.74\ H_2O$:

C, 61.30; H, 6.32; N, 5.96.

Found: C, 61.30; H, 6.37; N, 5.94.

In a process analogous to Example 10, the corresponding compounds were prepared:

EXAMPLE 10a

3-[3-Methyl-2-(phenethylcarbamoyl-methyl)-butyrylamino]-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid as a white solid.

Analysis calculated for $C_{32}H_{36}N_2O_7 \cdot 1.5\ H_2O$ (587.676):

C, 65.40; H, 6.69; N, 4.77.

Found: C, 65.23; H, 6.69; N, 4.74.

EXAMPLE 10b

3-(3-Carboxy-2-methyl-propionylamino)-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid

EXAMPLE 11

3-(2-Methyl-3-sulfamoyl-propionylamino)-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid

To solution of D-(-)-S-acetyl-β-mercaptoisobutyric acid (14.0 g, 86.4 mmol) in 125 mL of toluene at 0°C under N_2 was added dropwise 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 13.6 g, 89.5 mmol), and then benzyl bromide (15.3 g, 89.5 mmol) was added dropwise over a 5-minute period. The reaction was allowed to warm to room temperature overnight. The reaction was concentrated, diluted with saturated $NaHCO_3$ solution, and extracted with EtOAc (3×). The combined organic extract was washed with brine, dried ($MgSO_4$), filtered, and concentrated to give D-(-)-S-acetyl-β-mercaptoisobutyric acid, benzyl ester, which was carried on without further purification.

Chlorine gas was bubbled through a 0°C solution of D-(-)-S-acetyl-β-mercaptoisobutyric acid, benzyl ester (7.1 g, 20.5 mmol) in 80 mL of carbon tetrachloride:ethanol (9:1) for 90 minutes. The solution was concentrated. The resultant sulfonyl chloride was dissolved into 70 mL of CH_2Cl_2, cooled to 0°C and treated with dropwise addition of a solution of triethylamine (2.4 g, 24.6 mmol) and bis(*p*-methoxy-benzyl)amine (5.5 g, 21.5 mmol, J. Org. Chem., 1992;57:7065) in 10 mL of CH_2Cl_2. The solution was stirred at 0°C for 3 hours, concentrated, diluted with water, and extracted into EtOAc (3×). The combined organic extract was washed with brine, dried ($MgSO_4$), filtered, and concentrated. The resultant brown oil was chromatographed (MPLC, silica gel, 30% EtOAc in hexanes) to give the sulfonamide as a light yellow oil.

A solution of the sulfonamide (8.45g, 17 mmol) in THF was treated with 20% palladium on carbon and hydrogenated at 50 psig H_2 and room temperature for 4 hours. The sample was filtered through a pad of Celite and concentrated to give the sulfonamide acid as a colorless oil, which solidified upon standing.

To a solution of the sulfonamide acid (4.1 g, 10 mmol) and pyridine (0.8 g, 10 mmol) in 100 mL of CH_2Cl_2 at 0°C was added dropwise cyanuric fluoride (2.76 g, 20 mmol). The sample was stirred at 0°C for 2 hours, diluted with water,

and extracted into CH_2Cl_2 (2×). The combined CH_2Cl_2 extract was dried ($MgSO_4$), filtered, and concentrated. The resultant oil was dissolved into 100 mL of CH_2Cl_2, then treated with H-Asp(OtBu)OMe•HCl (4.08 g, 17 mmol) followed by dropwise addition of 4-methyl-morpholine (2.0 g, 20 mmol). The solution was stirred at room temperature for 12 hours, then partitioned between EtOAc and saturated $NaHCO_3$ solution. The organic extract was washed with saturated NaH_2PO_4 and brine solutions, dried ($MgSO_4$), and concentrated to give an oil which solidified upon standing.

The methyl ester (4.58 g, 7.73 mmol) was stirred in methanol (50 mL) and 0.5N aqueous NaOH (20 mL) overnight at room temperature. Methanol was removed in vacuo, and the residue was diluted with water (100 mL), then acidified with concentrated HCl and extracted with EtOAc. The organic layer was dried (Na_2SO_4) and concentrated to afford 3.7 g (83%) of the free acid as a foamy yellow solid.

To a solution of the acid (3.7 g, 6.4 mmol) and 4-methylmorpholine (0.65 g, 6.4 mmol) in 50 mL of THF at -42°C was added isobutyl chloroformate (0.89 g, 6.4 mmol) dropwise. After stirring 30 minutes, the reaction mixture was added to a solution of diazomethane in diethyl ether (~0.3 M, 100 mL) at 0°C. The reaction mixture was stirred for 2 hours at room temperature, then cooled to 0°C. A solution of 48% HBr (15 mL) and HOAc (15 mL) was added dropwise, and the reaction was stirred for 30 minutes at 0°C. The sample was diluted with diethyl ether and washed with water (2×) and saturated $NaHCO_3$ solution (2×). The organic layer was dried (Na_2SO_4) and concentrated to afford 3.88 g (97%) of the bromomethyl ketone as a yellow solid.

A mixture of bromomethyl ketone (0.624 g, 1.0 mmol), 1-naphthylacetic acid (0.372 g, 2.0 mmol), and potassium fluoride (0.145 g, 2.5 mmol) in 2.0 mL of anhydrous DMF was stirred at room temperature for 12 hours. The reaction mixture was diluted with EtOAc and washed successively with water (2×) and saturated $NaHCO_3$ solution. The organic layer was dried (Na_2SO_4), concentrated,

and the residue was chromatographed (MPLC, silica gel, hexanes-EtOAc [2:1]) to afford 0.470 g (62%) of di-*p*-methoxybenzyl sulfonamide as a white solid.

A mixture of di-*p*-methoxybenzyl sulfonamide (0.760 g, 1.0 mmol) and ammonium cerium (IV) nitrate (CAN, 4.39 g, 8.0 mmol) was stirred in 95% CH_3CN and 5% H_2O (20 mL) for 18 hours. The CH_3CN was removed in vacuo, the sample was diluted with EtOAc, and washed with saturated $NaHCO_3$ solution (2×). The organic layer was dried (Na_2SO_4), concentrated, and the residue was chromatographed (MPLC, silica gel, 50% EtOAc-50% hexanes) to afford 0.280 g (54%) of the desired primary sulfonamide tert-butyl ester.

The primary sulfonamide tert-butyl ester (0.375 g, 0.72 mmol) was treated with trifluoroacetic acid (5 mL) and CH_2Cl_2 (5 mL) for 1 hour at room temperature. The solvents were removed in vacuo to afford a yellow solid. The residue was recrystallized from CH_2Cl_2-hexanes to afford 0.090 g (27%) of 3-(2-methyl-3-sulfamoyl-propionylamino)-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid as an off-white solid.

Analysis calculated for $C_{21}H_{24}N_2O_8S_1 \cdot 0.27\ CF_3CO_2H$:

C, 52.23; H, 4.94; N, 5.66.

Found: C, 52.23; H, 5.07; N, 5.54.

INHIBITION STUDIES

Compounds of Formula I are inhibitors of ICE as demonstrated by measurement of K_i (μM) and IC_{50} (μM) using the protocol described herein. ICE (0.24 nM final concentration) is added to 400 μL of HGDE buffer (100 mM HEPES, 20% glycerol, 5 mM DTT, 0.5 mM EDTA) containing 15 μM substrate (Ac-Tyr-Val-Ala-Asp-AMC; K_M = 15 μM) plus vehicle (DMSO) or inhibitor at concentrations bracketing the K_i. Substrate hydrolysis is monitored for 300 seconds by observing the fluorescence of released AMC using excitation at 380 nm and emission at 460 nm. Mean rates of substrate hydrolysis are evaluated

by linear-regression analysis of the fluorescence vs time traces. To evaluate K_i, plots of percent inhibition vs inhibitor concentration are fit by non-linear regression to a reversible, competitive model:

$$\%\text{Inhibition} = \frac{100*[I]}{[I]+Ki*\left(1+\frac{[S]}{KM}\right)}$$

where the competition factor $(1 + [S]/K_M) = 2$.

PBMC Cellular Assay - IC_{50} Determinations

Further evidence that compounds of Formula I are inhibitors of ICE is provided by their ability to inhibit IL-1β production in human peripheral blood mononuclear cells (PBMCs) as described herein. PBMCs are isolated from heparinized blood by centrifugation over a Ficoll cushion, then washed three times with phosphate-buffered saline. PBMCs are suspended in a medium containing RPMI 1640 with glutamine, penicillin, streptomycin, and 2% human AB serum, then plated at 10^6 cells per well in 96-well flat bottom plates. PBMCs are stimulated overnight with 10 ng/mL of lipopolysaccharide (LPS, *E. coli* strain 0111:B4; Calbiochem) in the presence or absence of a compound of Formula I. Medium is harvested and the level of mature IL-1β was determined using an ELISA kit from R & D Systems. Compound inhibition (IC_{50}) is assessed by determining the concentration of agent which reduced IL-1β levels by 50%. Cells were cultured for an additional 4 hours in the presence of 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) to determine viability. Compound toxicity can, therefore, be assessed by determining the concentration of agent which kills 50% of the cells (TC_{50}).

ICE Colorimetric Dose-Response (IC_{50}) Assay

Diluted inhibitor stocks are prepared by two-fold serial dilution from a primary stock whose concentration is selected (based on screening results or on

prior attempts at IC_{50} evaluation) to achieve approximately 95% inhibition in the most concentrated well. Aliquots of each dilution are transferred to a microtitre plate in triplicate.

ICE enzyme is diluted to approximately 24 nM in HGE buffer (100 mM Hepes pH 7.5, 0.5 mM EDTA, 20% glycerol, 0.1% Bovine Serum Albumin (BSA), and activated by adding dithiothreitol (DTT) to a final concentration of 5 mM. The activated enzyme is then aliquoted into wells containing inhibitor or vehicle, and the plate is preincubated for 60 minutes at ambient temperature. Substrate (Ac-Tyr-Val-Ala-Asp-pNA) is added to each well to a final concentration of 50 μM, and plates are placed in the microtitre plate-reader thermostated to 25°C. Beginning 5 minutes after addition of substrate, absorbance (405 nm) of wells is monitored for 1 hour, and activity is calculated as the mean rate of change in absorbance during this interval.

Ich-2 (Caspase-4) Colorimetric Dose-Response (IC_{50}) Assay

Inhibition of Ich-2 enzyme is assayed as described above for ICE, except that enzyme is used at 64 nM, and 60 μM of the Ich-2-specific substrate Ac-Leu-Glu-Val-Asp-pNA is used instead of the ICE substrate Ac-Tyr-Val-Ala-Asp-pNA. The results of these tests are shown below in Table 1.

TABLE 1

Example Number	ICE K_i(μM)	ICE IC_{50} (μM)	PBMC IC_{50} (μM)	PBMC TC_{50} (μM)	Ich-2 (Caspase-4) IC_{50} (μM)
1	0.460	3.100	24.0	>100	3.60
1a	4.500	32.000	>100	>100	73.00
1b	4.100	30.000	--	--	25.00
1c	0.990	3.600	>100	>100	3.00
1d	1.700	0.686	>100	>100	2.00
1e	1.100	1.170	40.0	>100	0.93
1f	1.300	8.100	47.5	>100	26.00
1g	1.300	9.200	>100	>100	26.00
1h	6.000	35.000	--	--	38.00
1i	0.760	7.600	57.5	95.0	23.00
1j	0.600	6.500	47.5	>100	8.60
1k	1.900	8.500	>100	>100	13.00
1l	0.970	8.200	47.5	>100	--
1m	14.00	3.000	>100	>100	--
1n	76.00	6.000	--	--	7.00
1o	6.40	35.00	--	--	48.00
1p	2.80	1.100	>100	>100	3.90
1q	5.60	29.000	--	--	23.00
1r	3.90	9.70	50.0	>100	6.80
1s	8.10	66.60	--	--	53.00
1t	8.300	24.000	--	--	52.00
1u	16.00	50.00	--	--	--
1v	6.2	15.8			
1w	1.3	5.8	65	>100	
1x	9.1	32.2			
1y	5.6	12			
1z	4.4	12.5			
1aa	1.7	7.5	--		
1bb	7	19.5			
1cc	4.3	6.7	--		
1dd	2.1	12	--		
1ee	5	24	--		
1ff	7.625	14	27.5		
1gg	4.1	19	65		
1hh	9	38	90		
1ii	2.015	20.7	90		
1jj	6.9	16.6	>100		
1kk	21	0.92	--		
1ll	7.5	15	42.5		
1mm	2.64	3.9	55		
1nn	0.82	6.0	>100		

TABLE 1 (cont)

Example Number	ICE K_i(μM)	ICE IC_{50} (μM)	PBMC IC_{50} (μM)	PBMC TC_{50} (μM)	Ich-2 (Caspase-4) IC_{50} (μM)
1oo	1.2	9.5	>100		
1pp	1.1	13	>100		
1qq	3.1	1.2	>100		
1rr	2	4.6	45		
1ss	5.6	4.78	45		
1tt	8.75	43	>100		
1uu	3.3	3.1	37.5		
1vv	8.5	3.1	50		
1ww	20	1.6			
1xx	1.7	11.3	40		
1yy	7.7	1.06	>100		
1zz	37	3.3	>100		
1ccc	6.2	54.2	>100		
1ddd	2.2	7	67.5		
1eee	1.6	3.2	55		
1fff	2.4	23	85		
1ggg	3.1	9.5	>100		
2	0.272	0.846	35.0	>100	1.15
2a	0.850	5.50	65.0	>100	3.1
2b	1.700	4.100	35.0	>100	1.20
2c	20.000	2.800	>100	>100	--
2d	3.15	6.70	>100	>100	6.9
2e	2.90	3.80	>100	>100	16.7
3	0.066	0.082	7.0	>100	0.065
3a	5.2	1.05	>100		
3b	7.4	1.6	>100		
3c	0.084	0.043	9		
3d	0.077	0.078	19		
3e	0.0815	0.01	1.2		
3f	0.5	0.108	45		
3g	0.16	0.065	14.5		
3h	0.068	0.029	8		
3i	0.129	0.081	16		
3j	17	2	>100		
3k	0.79	0.2	29		
3l	0.92	0.3	70		
3m	1.8	3.8	>100		
3n	0.283	1.33	32.5		
3o	0.0024	0.0048	0.65		
3p	0.041	0.0575	5		
3q	0.092	0.0825	5		

TABLE 1 (cont)

Example Number	ICE K_i(μM)	ICE IC_{50} (μM)	PBMC IC_{50} (μM)	PBMC TC_{50} (μM)	Ich-2 (Caspase-4) IC_{50} (μM)
3r	0.048	0.10	7		0.074
3s	0.053	0.070	7.8		0.021
3t	0.17	0.54	12		0.05
3u	3.2	5.1	>100		1.9
3v	0.10	0.11	12		0.05
3w	3.8	7.7	>100		4.1
4	0.680	1.800	32.5	>100	17.00
4a	0.500	1.450	35.0	>100	1.20
4b	0.74	0.23	57.5		
4c	0.14	0.018	9.5		
4d	0.11	0.012	>100		
4e	0.17	0.068	7		
4f	0.21	0.107	16.5		
4g	0.6	0.15	44		
4h	1.7	2.38	65		
4i	0.17	0.068	7		
4j	0.189	0.096	25		
4k	1.6	1.4	>100		
4l	0.48	0.96	47.5		
5	1.4	0.835	90		
5a	0.072	0.102	23		
5b	5.55	1	>100		
5c	0.78	1.65	80		
5d	0.49	0.037	42.5		
5e	6.1	1.2	70		
5f	4.5	13.1	55		
5g	3.7	7.2	39		
5h	3.9	1.35	46.5		
5i	0.535	0.082	11		
5j	6.5	0.178	55		
5k	1.3	3.35	52.5		
5l	6.1	26.8	55		
5m	0.66	3.37	30		
5n	3.4	0.196	80		
5o	2.4	17.9	27.5		
5p	0.42	0.563	72.5		
5q	0.815	1.62	52.5		
5r	1.8	1.14	90		
5s	1.2	3.5	100		
5t	0.11	0.043	14		
5u	0.7	4.3	30		

TABLE 1 (cont)

Example Number	ICE K_i(μM)	ICE IC_{50} (μM)	PBMC IC_{50} (μM	PBMC TC_{50} (μM)	Ich-2 (Caspase-4) IC_{50} (μM)
5v	1.1	4.5	40		
5w	1.2	6.9	52.5		
5x	0.11	0.06	65		
5y	0.44	2.6	32.5		
6	0.000055	0.0019	1.6		
6a		0.0019	0.55		
6b	0.098	0.0215	9.5		
6c	0.00091	0.0051	4.3		
6d	0.0535	0.0075	6.8		
6e	0.001	0.0029	2.9		
6f	0.0015	0.0113	1.4		
6g	0.0027	0.0015	0.5		
6h	0.00012	0.0013	0.6		
6i	0.00016	0.00343	2.8		
6j	0.00005	0.0023	1		
6k	0.082	0.27	9.5		
6l	0.42	0.058	9.3		
6m	0.49	1.1	27.5		
6n	0.0002	0.0035	1.5		
6o	0.15	0.497	20		
7	0.000056	0.0025	0.43		
7a		0.0032	1.3		
7b	0.077	0.0023	0.93		
8	3.9	0.44	85		
8a	4	0.127	75		
8b	1.4	0.092	27.5		
9	0.48	0.33	30		
9a	0.11	0.095	30		
9b	0.1465	0.021636	24		
9c	0.1735	0.42797	22.7		
9d	0.067	0.40277	23.3		
9e	1.1	0.658	57.5		
9f	0.37	0.27	11		
9g	4.6	19	47.5		
9h	0.49	0.32	10		
9i	2.9	10	23.5		
9j	6.8	22	37.5		
9k	5	21.1	42.5		
9l	1.86	0.70227	26.7		
9m	0.8	0.23	22.5		
9n	2	12	52.5		

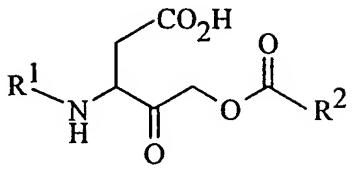
TABLE 1 (cont)

Example Number	ICE K_i(μM)	ICE IC_{50} (μM)	PBMC IC_{50} (μM)	PBMC TC_{50} (μM)	Ich-2 (Caspase-4) IC_{50} (μM)
9o	0.56	4	13		
9p	0.107	0.047	25		
9q	1.1	1	60		
9r	0.16	3.3	32.5		
9s	4.8	27.786	75		
9t	1.2	0.13825	24		
9u	1.6	7.3799	28.3		
9v	0.297	0.74924	27.7		
9w	0.1485	0.024696	37.5		
9x	0.342	0.75009	32.7		
9y	0.4575	0.058631	41.5		
9z	0.7105	4.5923	47.5		
9aa	0.0515	0.012147	15		
9bb	0.0565	0.0124	21.7		
9cc	0.0915	0.0248	33.5		
9dd	0.358	0.81376	35		
9ee	0.1845	1.2318	45		
9ff	0.06	0.0235595	24.7		
9gg	0.69	0.15775	24.3		
9hh	0.48	4.3431	27		

HEPES= 4-(2-hydroxymethyl)-1-piperazine ethane sulfonic acid
DTT = Dithiothreitol
EDTA = Ethylene diamine tetra acetic acid
Ac = Acetyl
Glu = Glutamic acid
Leu = Leucine
Tyr = Tyrosine
Val = Valine
Ala = Alanine
Asp = Aspartic Acid
AMC = 7-amino-4-methyl coumarin
pNA = Para nitroaniline
HOBT = 1-hydroxy benzotriazole
AA = An amino acid
Me = Methyl
Et = Ethyl
DMF = Dimethyl formamide
EDCI = N-ethyl-N′-dimethyl aminopropyl carbodiimide

CLAIMS

1. A compound of the Formula I



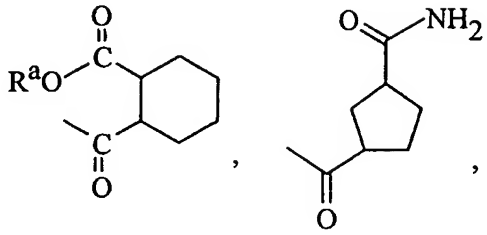
I

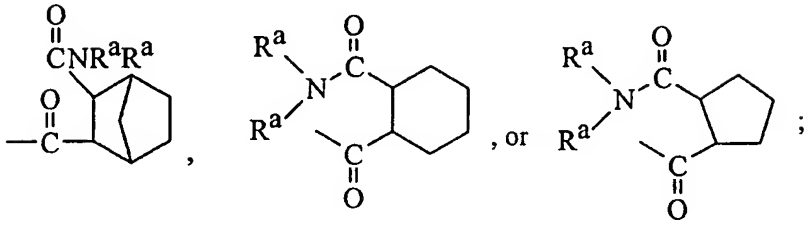
wherein R^1 is $R^3OC(=O)$-,

R^3CO-,

R^3SO_2-,

R^5NCHR^6CO-,





each R^a is independently hydrogen, C_1-C_6 alkyl, or -$(CH_2)_n$ aryl;

R^2 is -$(CRR)_n$-aryl,

-$(CRR)_n$-X-aryl,

-$(CRR)_n$-heteroaryl,

-$(CRR)_n$-X-heteroaryl,

$-(CRR)_n$-(substituted-heteroaryl),

$-(CRR)_n$-(substituted-aryl),

$-(CRR)_n$-X-(substituted-aryl),

$-(CRR)_n$-aryl-aryl,

$-(CRR)_n$-aryl-heteroaryl,

$-(CRR)_n$-aryl-$(CH_2)_n$-aryl,

$-(CRR)_n$-$CH(aryl)_2$,

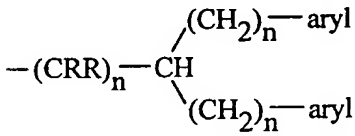
$-(CRR)_n$-cycloalkyl,

$-(CRR)_n$-X-cycloalkyl,

$-(CRR)_n$-heterocycle,

$-(CRR)_n$-X-heterocycle,

$-(CRR)_n$ substituted heterocycle,



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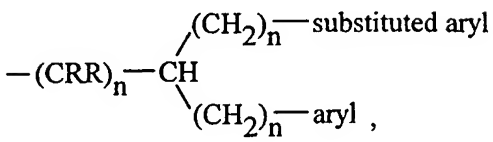

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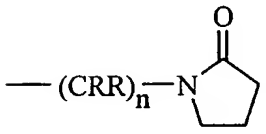

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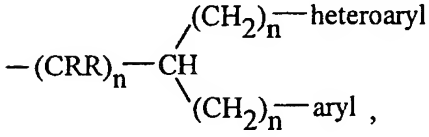

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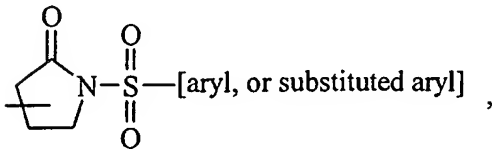

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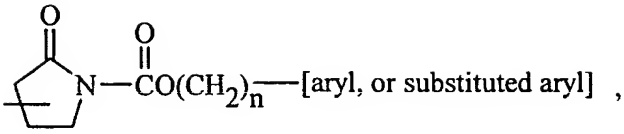
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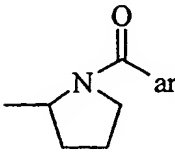
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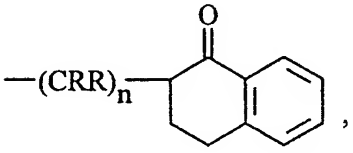
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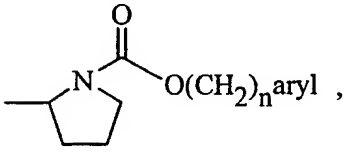
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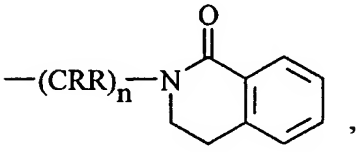
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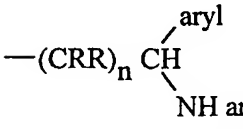
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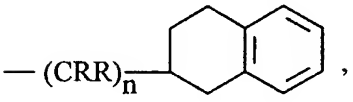
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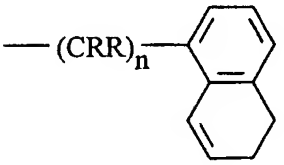
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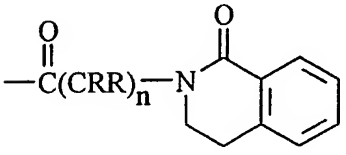
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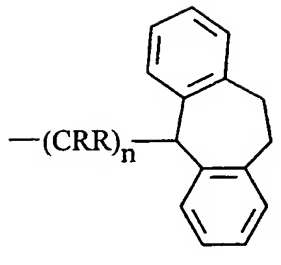

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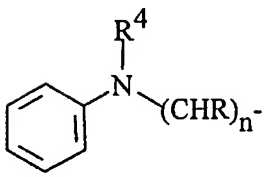

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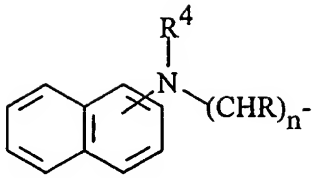


;

each R is independently hydrogen, C_1-C_6 alkyl, halogen or hydroxy;

X is O or S;

R^3 is C_1-C_6 alkyl,

aryl,

heteroaryl,

-$(CHR)_n$-aryl,

-$(CHR)_n$-heteroaryl,

-$(CHR)_n$-substituted heteroaryl,

-$(CHR)_n$-substituted aryl,

$$-(CRR)_nC(=O)R^a,$$

-$(CRR)_nS(CH_2)_n$-aryl,

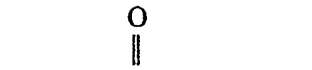
cycloalkyl,

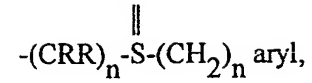
substituted cycloalkyl,

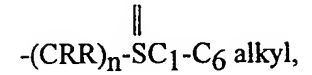
heterocycle,

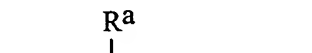
substituted heterocycle,

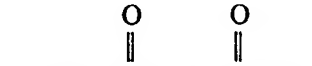
$$-(CRR)_nC(=O)NR^aR^a,$$

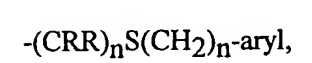


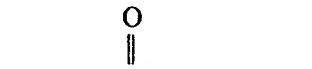


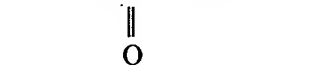


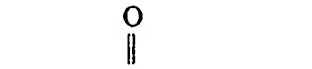


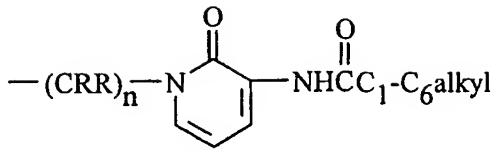


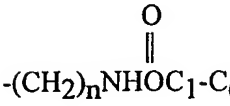


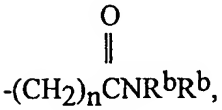


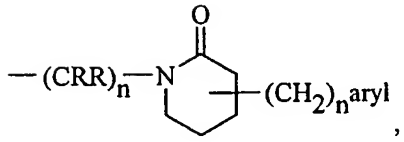


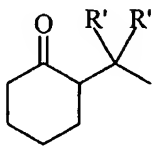


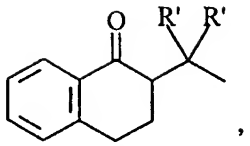


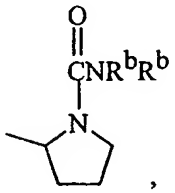


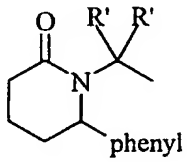


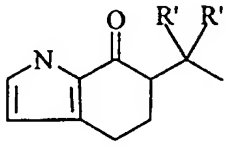


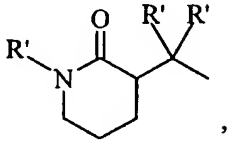


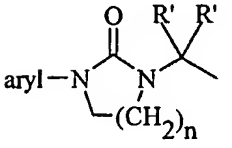


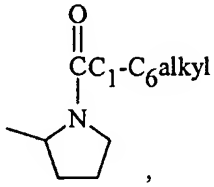


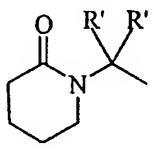


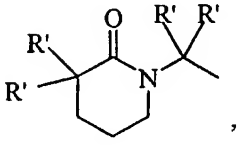


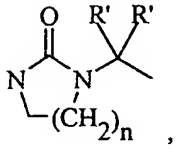


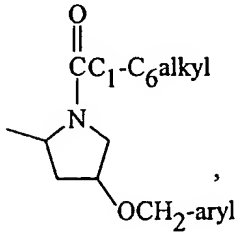


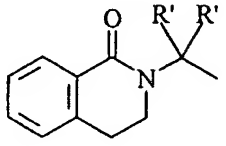


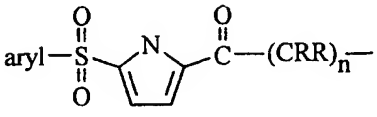


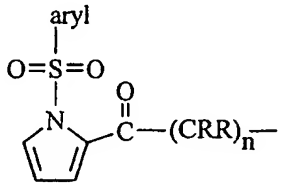












each R′ is independently C_1-C_6 alkyl,

C_1-C_6 alkylaryl,

aryl, or

hydrogen;

each J is independently

$-CO_2R^b$,

$-CONR^bR^b$,

$-SO_2NR^bR^b$, or

$-SO_2R^b$;

each R^b is independently hydrogen, C_1-C_6 alkyl, aryl, substituted aryl; arylalkyl, heteroarylalkyl, substituted arylalkyl, or substituted heteroarylalkyl;

R^4 is hydrogen,

C_1-C_6 alkyl,

$CH_3OC(=O)-$,

-phenyl, or

C_1-C_6 alkyl $C(=O)-$;

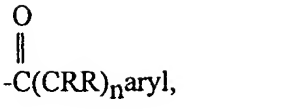
R^5 is C_1-C_6 alkyl-CO-,

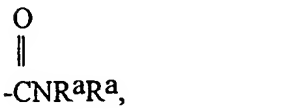
$-(CH_2)_n$ aryl,

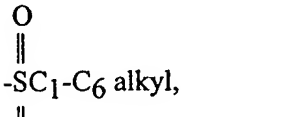
C_1-C_6-alkyl$OC(=O)-$,

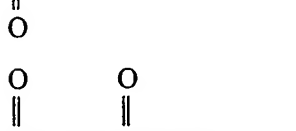
C_1-C_6-alkyl-X-$(CH_2)_nCO$,

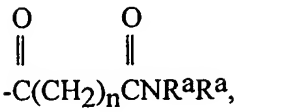
C_1-C_6-alkyl-X-$(CH_2)_nOC(=O)-$,

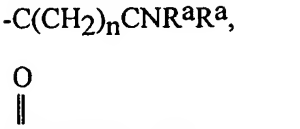


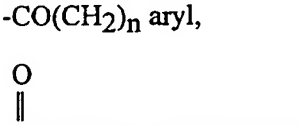


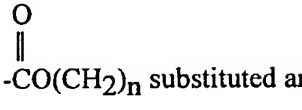


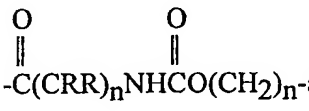


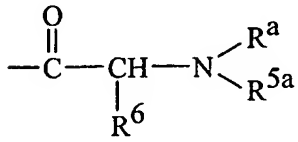






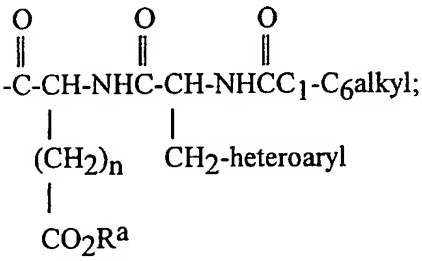




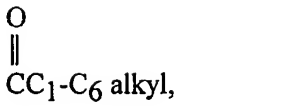


-$(CH_2)_nX(CH_2)_n$-aryl,

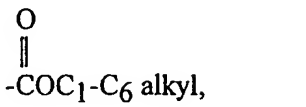
-C_1-C_6 alkyl X-C_1-C_6 alkyl aryl, or



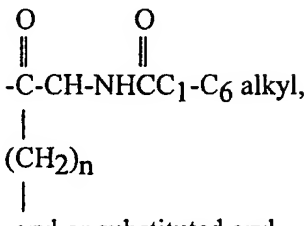
R^{5a} is



CC_1-C_6 alkyl,



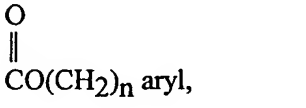
-COC_1-C_6 alkyl,



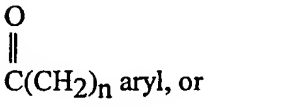
-C-CH-$NHCC_1$-C_6 alkyl,

$(CH_2)_n$

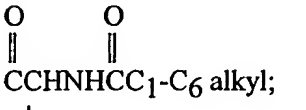
aryl or substituted aryl,



$CO(CH_2)_n$ aryl,



$C(CH_2)_n$ aryl, or



$CCHNHCC_1$-C_6 alkyl;

CH_2 heteroaryl

R^6 is hydrogen,

C_1-C_6 alkyl, -$(CH_2)_n$ aryl, -$(CH_2)_nCO_2R^a$, hydroxyl substituted C_1-C_6 alkyl, or imidazole substituted C_1-C_6 alkyl;

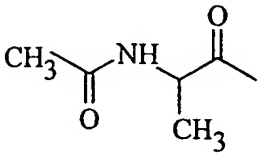
each n is independently 0 to 3, and the pharmaceutically acceptable, salts, esters, amides, and prodrugs thereof.

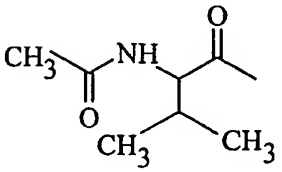
2. A compound according to Claim 1 wherein R^1 is phenyl-CH_2-  -.

3. A compound according to Claim 1 wherein R^1 is phenyl-SO_2-.

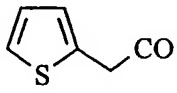
4. A compound according to Claim 1 wherein R^1 is CH_3-OC-.

5. A compound according to Claim 1 wherein R^1 is phenyl-CH_2CH_2-CO-.

6. A compound according to Claim 1 wherein R^1 is  .

7. A compound according to Claim 1 wherein R^1 is  .

8. A compound according to Claim 1 wherein R^1 is phenyl-CH_2-CO-.

9. A compound according to Claim 1 wherein R^1 is  .

10. A compound according to Claim 1 wherein each R^a is hydrogen.

11. A compound according to Claim 1 wherein R^2 is -$(CH_2)_n$-phenyl.

12. A compound according to Claim 1 wherein R^2 is -$(CH_2)_n$-naphthyl.

13. A compound according to Claim 1 wherein R^2 is -$(CH_2)_n$-O-phenyl.

14. A compound according to Claim 1 wherein R^2 is -$(CH_2)_n$-O-naphthyl.

15. A compound according to Claim 1 wherein R^2 is -$(CH_2)_n$-S-phenyl.

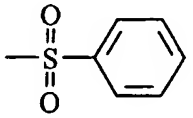
16. A compound according to Claim 1 wherein R^2 is-$(CH_2)_n$-CH(phenyl)$_2$.

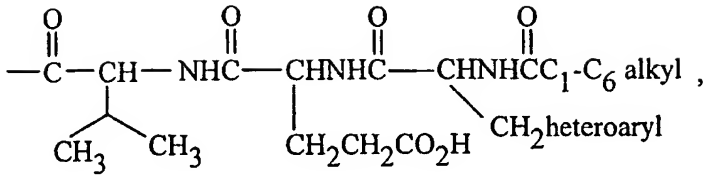
17. A compound according to Claim 1 wherein each R^a is hydrogen; R^1 is benzyloxycarbonyl; R^2 is aryl-X$(CRR)_n$-, aryl-$(CRR)_n$-, heteroaryl-$(CRR)_n$-, or cycloalkyl-$(CRR)_n$-; n is 1, 2, or 3; X is O or S; and R is hydrogen, methyl, or benzyl.

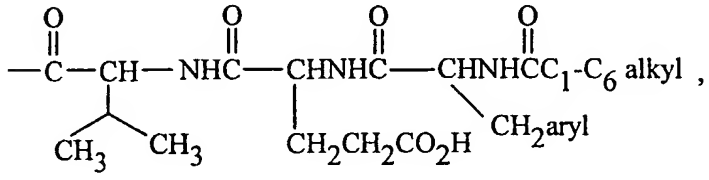
18. A compound according to Claim 1 wherein each R^a is hydrogen;
R^1 is benzyloxycarbonyl; and
R^2 is -$(CH_2)_n$-naphthyl,
-$(CH_2)_n$-phenyl,
-$(CH_2)_n$-cycloalkyl,
-$(CH_2)_nO(CH_2)_n$-naphthyl,
-$(CH_2)_nO(CH_2)_n$-phenyl, or
-$(CH_2)_nS(CH_2)_n$-phenyl.

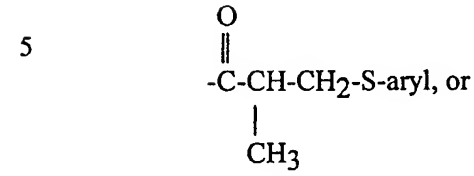
19. A compound according to Claim 1 wherein each R^a is hydrogen;
R^1 is benzyloxycarbonyl; and
R^2 is -CH_2-naphthyl.

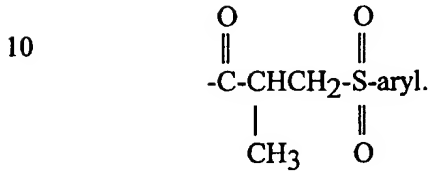
20. A compound in accordance with Claim 1 wherein each R^a is hydrogen;
R^2 is benzyloxycarbonyl,











21. A method of inhibiting interleukin-1β converting enzyme, the method comprising administering to a patient in need of inhibition of interleukin-1β converting enzyme a therapeutically effective amount of a compound of Claim 1.

22. A method of inhibiting Caspase-4, the method comprising administering to a patient in need of inhibition of Caspase-4 inhibition a Caspase-4 inhibiting amount of a compound of Claim 1.

23. A method of treating stroke, the method comprising administering to a patient having a stroke or having had a stroke a therapeutically effective amount of a compound of Claim 1.

24. A method of treating inflammatory diseases, the method comprising administering to a patient having an inflammatory disease a therapeutically effective amount of a compound of Claim 1.

25. The method of Claim 24 wherein the inflammatory disease is arthritis.

26. The method of Claim 24 wherein the inflammatory disease inflammatory bowel disease.

27. A method of treating reperfusion injury, the method of comprising administering to a patient having reperfusion injury a therapeutically effective amount of a compound of Claim 1.

28. A method of treating Alzheimer's disease, the method comprising administering to a patient having Alzheimer's disease a therapeutically effective amount of a compound of Claim 1.

29. A method of treating shigellosis, the method comprising administering to a patient having shigellosis a therapeutically effective amount of a compound of Claim 1.

30. A pharmaceutically acceptable composition that contains a compound of Claim 1.

31. The compounds:

3-Benzyloxycarbonylamino-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid;

3-Benzyloxycarbonylamino-4-oxo-5-(3-phenyl-propionyloxy)-pentanoic acid;

3-Benzyloxycarbonylamino-5-(3-cyclohexyl-propionyloxy)-4-oxo-pentanoic acid;

3-Benzyloxycarbonylamino-5-[(naphthalene-1-yl-oxy)-acetoxy]-4-oxo-pentanoic acid;

3-Benzyloxycarbonylamino-4-oxo-5-phenoxyacetoxy-pentanoic acid;

3-Benzyloxycarbonylamino-4-oxo-5-phenylsulfanylacetoxy-pentanoic acid;

3-Benzyloxycarbonylamino-5-[(6-methoxy-naphthalene-1-yl)-acetoxy]-4-oxo-pentanoic acid;

3-Benzyloxycarbonylamino-5-(naphthalene-2-yl-acetoxy)-4-oxo-pentanoic acid;

3-Benzyloxycarbonylamino-5-(3-naphthalene-2-yl-propionyloxy)-4-oxo-pentanoic acid;

3-Benzyloxycarbonylamino-5-(3,3-diphenyl-propionyloxy)-4-oxo-pentanoic acid;

3-Benzyloxycarbonylamino-5-[(1H-indol-3-yl)-acetoxy]-4-oxo-pentanoic acid;

3-Benzyloxycarbonylamino-5-(indol-1-yl-acetoxy)-4-oxo-pentanoic acid;

3-Benzyloxycarbonylamino-5-(2-naphthalene-1-yl-propionyloxy)-4-oxo-pentanoic acid;

3-Benzyloxycarbonylamino-4-oxo-5-[(2-oxo-pyrrolidin-1-yl)-acetoxy]-pentanoic acid;

5-[(Acetyl-phenyl-amino)-acetoxy]-3-benzyloxycarbonyl-amino-4-oxo-pentanoic acid;

3-Benzyloxycarbonylamino-5-(2-benzyl-3-phenyl-propionyloxy)-4-oxo-pentanoic acid;

3-Benzyloxycarbonylamino-5-(hydroxy-naphthalene-1-yl-acetoxy)-4-oxo-pentanoic acid;

3-Benzyloxycarbonylamino-4-oxo-5-[(phenyl-amino)-acetoxy]-pentanoic acid;

3-Benzyloxycarbonylamino-5-[(6-hydroxy-naphthalene-1-yl)-acetoxy]-4-oxo-pentanoic acid;

3-Benzyloxycarbonylamino-5-[3-(4-hydroxy-phenyl)-2-naphthalene-1-yl-propionyloxy)-4-oxo-pentanoic acid;

(S)-3-Benzyloxycarbonylamino-4-oxo-5-phenylacetoxy-pentanoic acid;

(S)-3-Benzyloxycarbonylamino-4-oxo-5-(4-phenyl-butyryloxy)-pentanoic acid;

3-Benzyloxycarbonylamino-4-oxo-5-[(4-phenyl-naphthalen-1-yl)-acetoxy]-pentanoic acid;

3-Benzyloxycarbonylamino-5-[(4-methyl-naphthalen-1-yl)-acetoxy]-4-oxo-pentanoic acid;

3-Benzyloxycarbonylamino-4-oxo-5-[(4-thiophen-2-yl-naphthalen-1-yl)-acetoxy]-pentanoic acid;

3-Benzyloxycarbonylamino-5-[(4-fluoro-naphthalen-1-yl)-acetoxy]-4-oxo-pentanoic acid;

3-Benzyloxycarbonylamino-5-[(2-methyl-naphthalen-1-yl)-acetoxy]-4-oxo-pentanoic acid;

3-Benzyloxycarbonylamino-5-[(2-fluoro-naphthalen-1-yl)-acetoxy]-4-oxo-pentanoic acid;

5-(Benzofuran-4-yl-acetoxy)-3-benzyloxycarbonylamino-4-oxo-pentanoic acid;

5-(Benzo[b]thiophen-7-yl-acetoxy)-3-benzyloxycarbonylamino-4-oxo-pentanoic acid;

5-(Benzo[b]thiophen-4-yl-acetoxy)-3-benzyloxycarbonylamino-4-oxo-pentanoic acid;

5-[(4-Benzyl-naphthalen-1-yl)-acetoxy]-3-benzyloxycarbonylamino-4-oxo-pentanoic acid;

3-Benzyloxycarbonylamino-5-[(3,4-dihydro-naphthalen-1-yl)-acetoxy]-4-oxo-pentanoic acid;

3-Benzyloxycarbonylamino-5-[(5-bromo-1H-indol-3-yl)-acetoxy]-4-oxo-pentanoic acid;

3-Benzyloxycarbonylamino-5-(3,4-diphenyl-butyryloxy)-4-oxo-pentanoic acid;

3-Benzyloxycarbonylamino-4-oxo-5-(3-phenyl-3-phenylamino-propionyloxy)-pentanoic acid;

3-Benzyloxycarbonylamino-4-oxo-5-[(1,2,3,4-tetrahydro-naphthalen-2-yl)-acetoxy]-pentanoic acid;

3-Benzyloxycarbonylamino-5-[(1-methanesulfonyl-piperidin-4-yl)-acetoxy]-4-oxo-pentanoic acid;

3-Benzyloxycarbonylamino-4-oxo-5-[(2,3,5,6-tetramethyl-phenyl)-acetoxy]-pentanoic acid;

5-(Benzothiazol-4-yl-acetoxy)-3-benzyloxycarbonylamino-4-oxo-pentanoic acid;

5-(Benzofuran-3-yl-acetoxy)-3-benzyloxycarbonylamino-4-oxo-pentanoic acid;

5-(Benzo[b]thiophen-3-yl-acetoxy)-3-benzyloxycarbonylamino-4-oxo-pentanoic acid;

3-Benzyloxycarbonylamino-4-oxo-5-(3-phenyl-3-pyridin-2-yl-propionyloxy)-pentanoic acid;

3-Benzyloxycarbonylamino-5-[(2,3-dichloro-phenyl)-acetoxy]-4-oxo-pentanoic acid;

3-Benzyloxycarbonylamino-5-[(5-methyl-naphthalen-1-yl)-acetoxy]-4-oxo-pentanoic acid;

3-Benzyloxycarbonylamino-5-[(2-iodo-phenyl)-acetoxy]-4-oxo-pentanoic acid;

3-Benzyloxycarbonylamino-4-oxo-5-(3-pyridin-3-yl-propionyloxy)-pentanoic acid;

3-Benzyloxycarbonylamino-5-[(5-methoxy-naphthalen-1-yl)-acetoxy]-4-oxo-pentanoic acid;

3-Benzyloxycarbonylamino-5-[(8-methyl-naphthalen-1-yl)-acetoxy]-4-oxo-pentanoic acid;

3-Benzyloxycarbonylamino-5-[(9H-fluoren-9-yl)-acetoxy]-4-oxo-pentanoic acid;

3-Benzyloxycarbonylamino-5-[(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-acetoxy]-4-oxo-pentanoic acid;

5-Oxo-1-(toluene-4-sulfonyl)-pyrrolidine-2-carboxylic acid 3-benzyloxycarbonylamino-4-carboxy-2-oxo-butyl ester;

5-Oxo-pyrrolidine-1,2-dicarboxylic acid 1-benzyl ester 2-(3-benzyloxycarbonylamino-4-carboxy-2-oxo-butyl) ester;

1-Benzoyl-pyrrolidine-2-carboxylic acid 3-benzyloxycarbonylamino-4-carboxy-2-oxo-butyl ester;

Pyrrolidine-1,2-dicarboxylic acid 1-benzyl ester 2-(3-benzyloxycarbonylamino-4-carboxy-2-oxo-butyl) ester;

3-Benzyloxycarbonylamino-5-(2-benzyl-3-phenyl-propionyloxy)-4-oxo-pentanoic acid;

3-Benzyloxycarbonylamino-5-[(5-cyano-naphthalen-1-yl)-acetoxy]-4-oxo-pentanoic acid;

3-Benzyloxycarbonylamino-4-oxo-5-(3-phenyl-3-pyridin-3-yl-propionyloxy)-pentanoic acid;

3-Benzyloxycarbonylamino-4-oxo-5-(3-phenyl-3-pyridin-4-yl-propionyloxy)-pentanoic acid; and

3-Benzyloxycarbonylamino-4-oxo-5-[(1-oxo-3,4-dihydro-1H-isoquinolin-2-yl)-acetoxy]-pentanoic acid.

32. The compounds:

3-Benzenesulfonylamino-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid;

3-Methoxycarbonylamino-5-(naphthalene-1-yl-acetoxy)-4-oxo-pentanoic acid;

5-(Naphthalene-1-yl-acetoxy)-4-oxo-3-(3-phenyl-propionylamino)-pentanoic acid;

3-Methoxycarbonylamino-4-oxo-5-phenoxyacetoxy-pentanoic acid; and

3-(2-Methanesulfonyl-1-methyl-ethylsulfanylamino)-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid.

33. The compounds:

[S-(R*,R*)]-3-(2-Acetylamino-propionylamino)-5-(naphthalene-1-yl-acetoxy)-4-oxo-pentanoic acid;

5-(Naphthalen-1-yl-acetoxy)-4-oxo-3-[(thiophene-3-carbonyl)-amino]-pentanoic acid;

3-[(Furan-3-carbonyl)-amino]-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid;

5-(Naphthalen-1-yl-acetoxy)-4-oxo-3-[2-(4-phenyl-butyrylamino)-propylamino]-pentanoic acid;

3-(2-Methanesulfonylamino-propionylamino)-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid;

3-[2-(2-Acetylamino-4-phenyl-butyrylamino)-propionylamino]-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid;

3-(2-Acetylamino-butyrylamino)-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid;

3-[2-(4-Carbamoyl-butyrylamino)-propionylamino]-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid;

3-(2-Benzyloxycarbonylamino-propionylamino)-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid;

5-(Naphthalen-1-yl-acetoxy)-4-oxo-3-(2-ureido-propionylamino)-pentanoic acid;

3-(2-Acetylamino-propionylamino)-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid;

3-[(1-Acetyl-pyrrolidine-2-carbonyl)-amino]-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid;

3-(2-Methyl-3-oxo-3-thiophen-2-yl-propionylamino)-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid;

3-(2-Acetylamino-acetylamino)-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid;

3-(2-Acetylamino-propionylamino)-5-(3,3-diphenyl-propionyloxy)-4-oxo-pentanoic acid;

3-[2-(2-Acetylamino-4-carboxy-butyrylamino)-propionylamino]-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid;

5-(Naphthalen-1-yl-acetoxy)-4-oxo-3-[2-(3-phenyl-propionylamino)-propionylamino]-pentanoic acid;

3-[2-(3-Methyl-butyrylamino)-propionylamino]-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid;

3-[(1-Acetyl-4-benzyloxy-pyrrolidine-2-carbonyl)-amino]-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid;

3-(4-Carbamoyl-butyrylamino)-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid; and

3-[2-(1-Methyl-1H-imidazol-4-yl)-acetylamino]-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid.

34. The compounds:

(S)-5-(Naphthalene-1-yl-acetoxy)-4-oxo-3-phenylacetylamino-pentanoic acid;

(S)-5-(Naphthalene-1-yl-acetoxy)-4-oxo-3-(2-thiophene-2-yl-acetylamino)-pentanoic acid;

3-[(2-Carbamoyl-cyclopentanecarbonyl)-amino]-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid;

3-[(3-Carbamoyl-bicyclo[2.2.1]heptane-2-carbonyl)-amino]-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid;

3-(3-Methanesulfonyl-2-methyl-propionylamino)-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid;

3-(3-Benzenesulfonyl-2-methyl-propionylamino)-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid;

3-Butyrylamino-5-(naphthalen-2-yl-acetoxy)-4-oxo-pentanoic acid;

3-Acetylamino-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid;

3-(3-Methanesulfonyl-2-methyl-propionylamino)-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid;

3-(3-Methyl-butyrylamino)-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid;

3-(3-Carbamoyl-propionylamino)-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid;

[S-(R*,R*)]-3-(3-Acetylsulfanyl-2-methyl-propionylamino)-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid; and

trans-3-[(3-Carbamoyl-cyclopentanecarbonyl)-amino]-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid.

35. The compounds:

3-(1,2,3,4-tetrahydro-1-oxo-isoquinoline-2-yl)-acetamino-5-(naphthalene-1-yl acetoxy)-4-oxo-pentanoic acid;

3-(2-Methyl-3-phenethylcarbamoyl-propionylamino)-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid;

5-(Naphthalen-2-yl-acetoxy)-4-oxo-3-[2-(2-oxo-6-phenyl-piperidin-1-yl)-acetylamino]-pentanoic acid;

5-(Naphthalen-1-yl-acetoxy)-4-oxo-3-[2-(2-oxo-6-phenyl-piperidin-1-yl)-acetylamino]-pentanoic acid;

3-[3-Methyl-2-(3-phenyl-propionylamino)-butyrylamino]-4-oxo-5-[(1-oxo-1,2,3,4-tetrahydro-naphthalen-2-yl)-acetoxy]-pentanoic acid;

5-(Naphthalen-2-yl-acetoxy)-4-oxo-3-[2-(1-oxo-3,4-dihydro-1H-isoquinolin-2-yl)-acetylamino]-pentanoic acid;

5-(2-Benzyl-3-phenyl-propionyloxy)-4-oxo-3-[2-(1-oxo-3,4-dihydro-1H-isoquinolin-2-yl)-acetylamino]-pentanoic acid;

5-(2-Benzyl-3-phenyl-propionyloxy)-4-oxo-3-[2-(2-oxo-6-phenyl-piperidin-1-yl)-acetylamino]-pentanoic acid;

5-(Naphthalen-1-yl-acetoxy)-4-oxo-3-[2-(1-oxo-1,2,3,4-tetrahydro-naphthalen-2-yl)-acetylamino]-pentanoic acid;

5-(Naphthalen-1-yl-acetoxy)-4-oxo-3-[2-(1-oxo-3,4-dihydro-1H-isoquinolin-2-yl)-propionylamino]-pentanoic acid;

5-(Naphthalen-2-yl-acetoxy)-4-oxo-3-[2-(1-oxo-3,4-dihydro-1H-isoquinolin-2-yl)-propionylamino]-pentanoic acid;

3-[4-(1-Benzenesulfonyl-1H-pyrrol-2-yl)-4-oxo-butyrylamino]-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid;

5-(2-Benzyl-3-phenyl-propionyloxy)-4-oxo-3-[2-(1-oxo-1,2,3,4-tetrahydro-naphthalen-2-yl)-acetylamino]-pentanoic acid;

5-(2-Benzyl-3-phenyl-propionyloxy)-4-oxo-3-[2-(1-oxo-3,4-dihydro-1H-isoquinolin-2-yl)-propionylamino]-pentanoic acid;

4-Oxo-3-[2-(1-oxo-3,4-dihydro-1H-isoquinolin-2-yl)-propionylamino]-5-[(1-oxo-1,2,3,4-tetrahydro-naphthalen-2-yl)-acetoxy]-pentanoic acid;

3-[4-(1-Benzenesulfonyl-1H-pyrrol-2-yl)-4-oxo-butyrylamino]-5-(2-benzyl-3-phenyl-propionyloxy)-4-oxo-pentanoic acid;

4-Oxo-5-[(1-oxo-1,2,3,4-tetrahydro-naphthalen-2-yl)-acetoxy]-3-[2-(1-oxo-1,2,3,4-tetrahydro-naphthalen-2-yl)-acetylamino]-pentanoic acid;

5-(Naphthalen-1-yl-acetoxy)-4-oxo-3-[2-(2-oxo-3-phenyl-imidazolidin-1-yl)-propionylamino]-pentanoic acid;

5-(Naphthalen-1-yl-acetoxy)-4-oxo-3-[2-(2-oxo-3-phenyl-tetrahydro-pyrimidin-1-yl)-propionylamino]-pentanoic acid;

5-(Naphthalen-1-yl-acetoxy)-4-oxo-3-[2-(2-oxo-3-phenyl-tetrahydro-pyrimidin-1-yl)-acetylamino]-pentanoic acid;

3-(2-Acetylamino-3-methyl-butyrylamino)-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid;

3-(2-Acetylamino-3-methyl-butyrylamino)-5-(2-benzyl-3-phenyl-propionyloxy)-4-oxo-pentanoic acid;

3-(2-Acetylamino-3-methyl-butyrylamino)-5-(3-benzyl-4-phenyl-butyryloxy)-4-oxo-pentanoic acid;

3-(2-Acetylamino-3-methyl-butyrylamino)-5-(4-benzyl-5-phenyl-pentanoyloxy)-4-oxo-pentanoic acid;

3-(2-Acetylamino-3-methyl-butyrylamino)-4-oxo-5-[(1-oxo-1,2,3,4-tetrahydro-naphthalen-2-yl)-acetoxy]-pentanoic acid;

5-(3-Benzyl-4-phenyl-butyryloxy)-3-[3-methyl-2-(3-phenyl-propionylamino)-butyrylamino]-4-oxo-pentanoic acid;

3-[2-(3-Acetylamino-2-oxo-2H-pyridin-1-yl)-acetylamino]-5-(3,3-diphenyl-propionyloxy)-4-oxo-pentanoic acid; and

3-[2-(3-Acetylamino-2-oxo-2H-pyridin-1-yl)-acetylamino]-5-(2-benzyl-3-phenyl-propionyloxy)-4-oxo-pentanoic acid.

36. The compounds:

3-[2-(2-Benzyloxycarbonylamino-4-carboxy-butyrylamino)-3-methyl-butyrylamino]-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid;

3-[2-(2-Benzyloxycarbonylamino-3-methyl-butyrylamino)-propionylamino]-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid;

3-(2-Acetylamino-3-methyl-butyrylamino)-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid;

3-[2-(2-Benzyloxycarbonylamino-3-methyl-butyrylamino)-propionylamino]-5-(3,3-diphenyl-propionyloxy)-4-oxo-pentanoic acid;

3-[2-(2-Benzyloxycarbonylamino-3-methyl-butyrylamino)-propionylamino]-5-(2-benzyl-3-phenyl-propionyloxy)-4-oxo-pentanoic acid;

3-[2-(2-Benzyloxycarbonylamino-3-methyl-butyrylamino)-propionylamino]-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid;

5-(2-Benzyl-3-phenyl-propionyloxy)-3-{2-[4-carboxy-2-(3-phenyl-propionylamino)-butyrylamino]-3-methyl-butyrylamino}-4-oxo-pentanoic acid;

3-(2-Benzyloxycarbonylamino-3-methyl-butyrylamino)-5-(3,3-diphenyl-propionyloxy)-4-oxo-pentanoic acid;

3-(2-Acetylamino-3-hydroxy-butyrylamino)-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid;

3-(2-Acetylamino-3-hydroxy-butyrylamino)-5-(3,3-diphenyl-propionyloxy)-4-oxo-pentanoic acid;

3-(2-{2-[2-Acetylamino-3-(1H-indol-3-yl)-propionylamino]-4-carboxy-butyrylamino}-3-methyl-butyrylamino)-5-(2-benzyl-3-phenyl-propionyloxy)-4-oxo-pentanoic acid; and

5-(3,3-Diphenyl-propionyloxy)-4-oxo-3-[2-(4-phenyl-butyrylamino)-propionylamino]-pentanoic acid.

37. The compounds:

3-(2-{2-[2-Acetylamino-3-(1H-indol-3-yl)-propionylamino]-4-carboxy-butyrylamino}-3-methyl-butyrylamino)-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid; and

3-(2-{2-[2-Acetylamino-3-(4-hydroxy-phenyl)-propionylamino]-4-carboxy-butyrylamino}-3-methyl-butyrylamino)-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid.

38. The compounds:

3-[(2-Carboxy-cyclohexanecarbonyl)-amino]-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid;

3-[(2-Methoxycarbonyl-cyclohexanecarbonyl)-amino]-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid; and

3-[(2-Carbamoyl-cyclohexanecarbonyl)-amino]-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid.

39. The compounds:

3-(3-Benzylsulfanyl-2-methyl-propionylamino)-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid;

3-(2-Methyl-3-phenylmethanesulfonyl-propionylamino)-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid;

3-[3-(2-Carboxy-ethanesulfanyl)-2-methyl-propionylamino]-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid;

5-(2-Benzyl-3-phenyl-propionyloxy)-3-[3-(2-carboxy-ethanesulfonyl)-2-methyl-propionylamino]-4-oxo-pentanoic acid;

5-(2-Benzyl-3-phenyl-propionyloxy)-3-[3-(3-carboxy-propane-1-sulfinyl)-2-methyl-propionylamino]-4-oxo-pentanoic acid;

5-(Naphthalen-1-yl-acetoxy)-4-oxo-3-(2-phenylmethanesulfanyl-propionylamino)-pentanoic acid;

3-(2-Methyl-3-phenylsulfanyl-propionylamino)-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid;

5-(2-Benzyl-3-phenyl-propionyloxy)-3-(2-methyl-3-phenylsulfanyl-propionylamino)-4-oxo-pentanoic acid;

3-(2-Methyl-3-phenethylsulfanyl-propionylamino)-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid;

5-(2-Benzyl-3-phenyl-propionyloxy)-3-(2-methyl-3-phenethylsulfanyl-propionylamino)-4-oxo-pentanoic acid;

5-(2-Benzyl-3-phenyl-propionyloxy)-3-(3-benzylsulfanyl-2-methyl-propionylamino)-4-oxo-pentanoic acid;

5-(2-Benzyl-3-phenyl-propionyloxy)-3-(2-benzylsulfanyl-propionylamino)-4-oxo-pentanoic acid;

3-[2-Methyl-3-(3-phenyl-propylsulfanyl)-propionylamino]-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid;

3-(3-Benzenesulfonyl-2-methyl-propionylamino)-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid;

3-(3-Benzenesulfonyl-2-methyl-propionylamino)-5-(2-benzyl-3-phenyl-propionyloxy)-4-oxo-pentanoic acid;

5-(2-Benzyl-3-phenyl-propionyloxy)-3-[2-methyl-3-(2-phenyl-ethanesulfonyl)-propionylamino]-4-oxo-pentanoic acid;

3-[2-Methyl-3-(2-phenyl-ethanesulfonyl)-propionylamino]-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid;

5-(Naphthalen-1-yl-acetoxy)-4-oxo-3-(2-phenylmethanesulfonyl-propionylamino)-pentanoic acid;

5-(2-Benzyl-3-phenyl-propionyloxy)-3-(2-methyl-3-phenylmethanesulfonyl-propionylamino)-4-oxo-pentanoic acid;

5-(2-Benzyl-3-phenyl-propionyloxy)-4-oxo-3-(2-phenylmethanesulfonyl-propionylamino)-pentanoic acid;

3-[2-Methyl-3-(3-phenyl-propane-1-sulfonyl)-propionylamino]-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid;

5-(2-Benzyl-3-phenyl-propionyloxy)-3-[2-methyl-3-(3-phenyl-propane-1-sulfonyl)-propionylamino]-4-oxo-pentanoic acid;

5-(2-Benzyl-3-phenyl-propionyloxy)-3-[3-(2-carboxy-ethylsulfanyl)-2-methyl-propionylamino]-4-oxo-pentanoic acid;

3-[3-(3-Carboxy-propylsulfanyl)-2-methyl-propionylamino]-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid;

5-(2-Benzyl-3-phenyl-propionyloxy)-3-[3-(3-carboxy-propylsulfanyl)-2-methyl-propionylamino]-4-oxo-pentanoic acid;

3-(3-Carboxymethylsulfanyl-2-methyl-propionylamino)-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid;

5-(2-Benzyl-3-phenyl-propionyloxy)-3-(3-carboxymethylsulfanyl-2-methyl-propionylamino)-4-oxo-pentanoic acid;

3-[3-(2-Carboxy-ethanesulfonyl)-2-methyl-propionylamino]-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid;

3-[3-(3-Carboxy-propane-1-sulfonyl)-2-methyl-propionylamino]-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid;

3-(3-Carboxymethanesulfonyl-2-methyl-propionylamino)-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid;

5-(2-Benzyl-3-phenyl-propionyloxy)-3-[3-(3-carboxy-propane-1-sulfonyl)-2-methyl-propionylamino]-4-oxo-pentanoic acid;

5-(2-Benzyl-3-phenyl-propionyloxy)-3-(3-carboxymethanesulfonyl-2-methyl-propionylamino)-4-oxo-pentanoic acid;

3-[3-(3-Carboxy-propane-1-sulfinyl)-2-methyl-propionylamino]-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid;

3-[2-Methyl-3-(3-phenyl-propane-1-sulfinyl)-propionylamino]-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid; and

5-(2-Benzyl-3-phenyl-propionyloxy)-3-[2-methyl-3-(3-phenyl-propane-1-sulfinyl)-propionylamino]-4-oxo-pentanoic acid.

40. The compounds:

3-[3-Methyl-2-(phenethylcarbamoyl-methyl)-butyrylamino]-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid; and

3-(3-Carboxy-2-methyl-propionylamino)-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid.

41. The compound:

3-(2-Methyl-3-sulfamoyl-propionylamino)-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid.

42. The compounds:

3-(3-Carbamoyl-2-methyl-propionylamino)-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid;

3-(2-Benzyloxycarbonylamino-3-methyl-naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid;

3-[(2-Carbamoyl-cyclopentanecarbonyl)-amino]-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid;

3-[(1-Carbamoyl-pyrrolidine-2-carbonyl)-amino]-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid;

3-(2-{2-[2-Acetylamino-3-(4-hydroxy-phenyl)-propionylamino]-4-carboxy-butyrylamino}-3-methyl-butyrylamino)-5-(2-benzyl-3-phenyl-propionyloxy)-4-oxo-pentanoic acid;

3-(3-Carbamoyl-2-methyl-propionylamino)-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid;

3-(2-Carbamoylmethyl-3-methyl-butyrylamino)-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid;

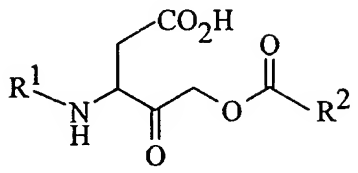
3-(3-Benzyloxy-2-ureido-propionylamino)-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid;

3-[2-(2-Benzyloxycarbonylamino-4-carboxy-butyrylamino)-3-methyl-butyrylamino]-5-(2-benzyl-3-phenyl-propionyloxy)-4-oxo-pentanoic acid;

3-{2-[4-Carboxy-2-(3-phenyl-propionylamino)-butyrylamino]-3-methyl-butyrylamino}-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid; and

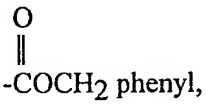
3-[2-(2-Acetylamino-4-carboxy-butyrylamino)-3-methyl-butyrylamino]-5-(naphthalen-1-yl-acetoxy)-4-oxo-pentanoic acid.

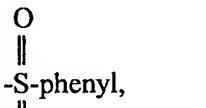
43. A compound of the Formula I

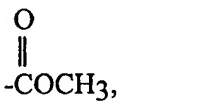


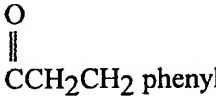
I

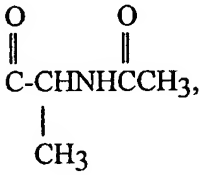
wherein R^1 is

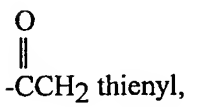


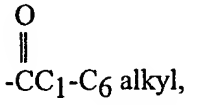




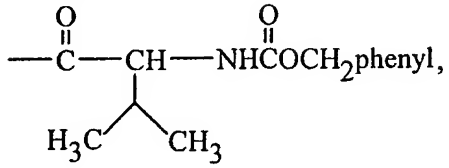


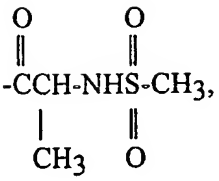


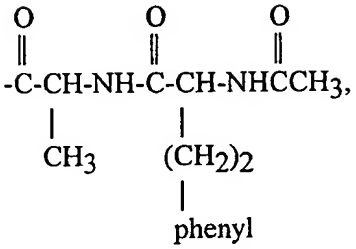


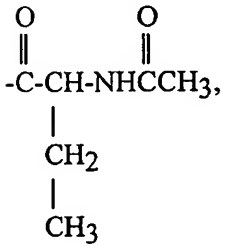


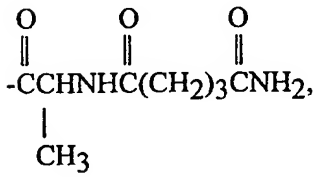
-(CH$_2$)$_3$ phenyl,

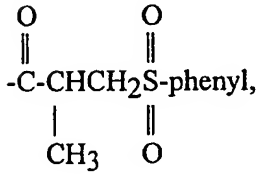


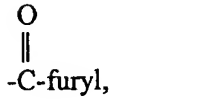


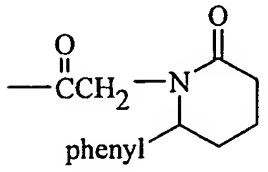


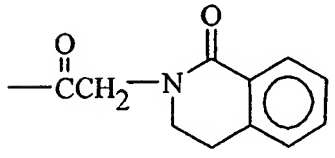


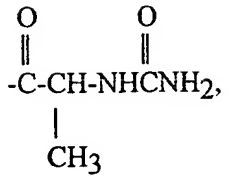


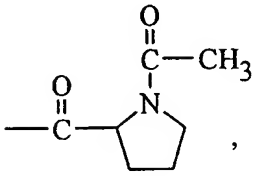


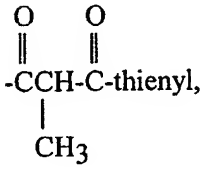


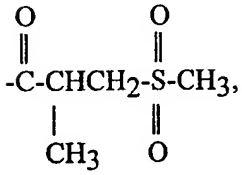


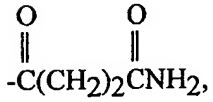


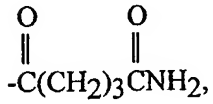


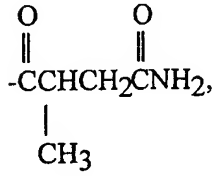


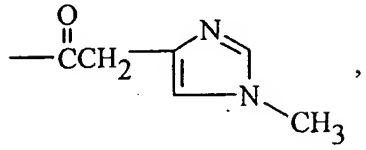


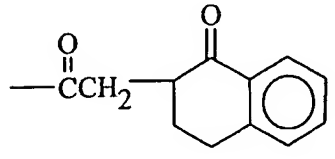


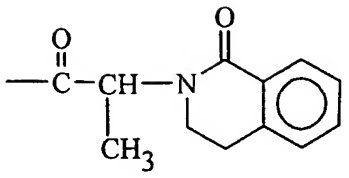


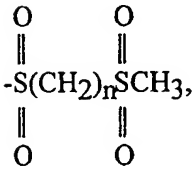


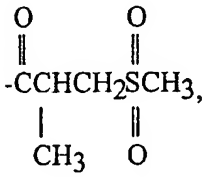


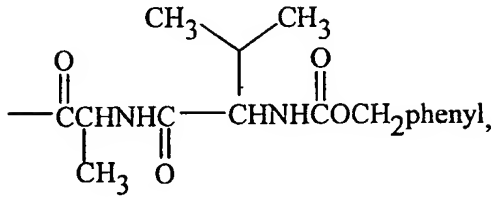


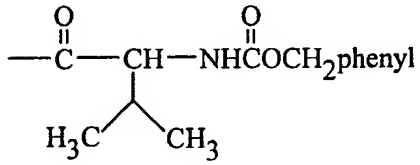


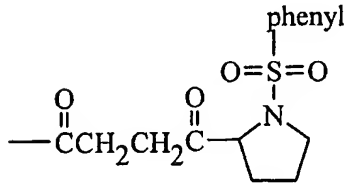


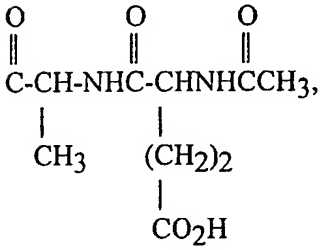


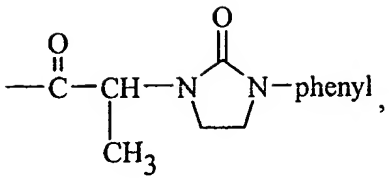


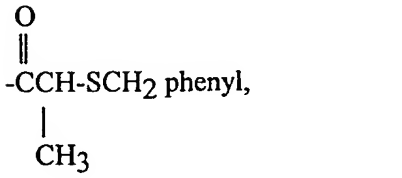


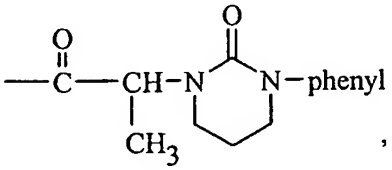


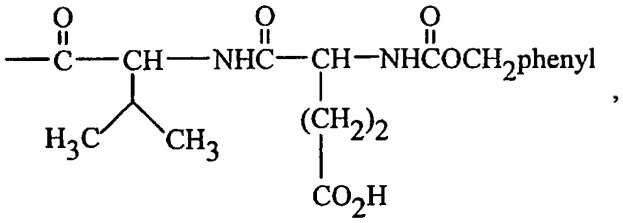


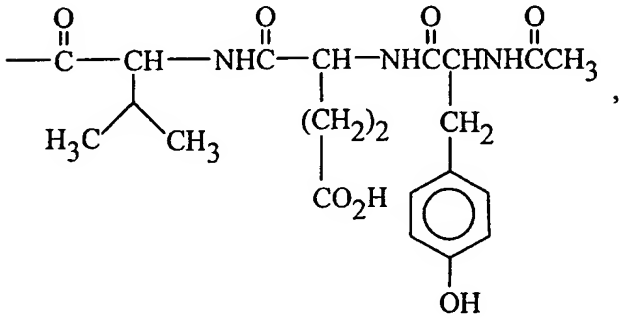


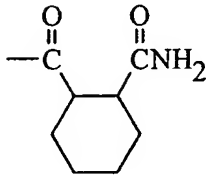


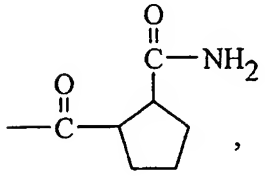


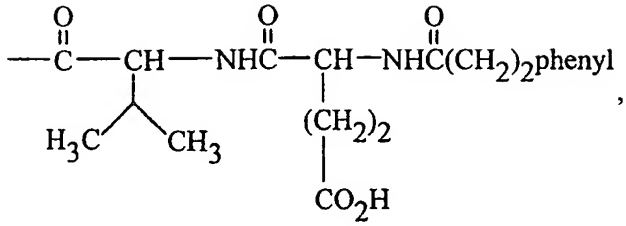


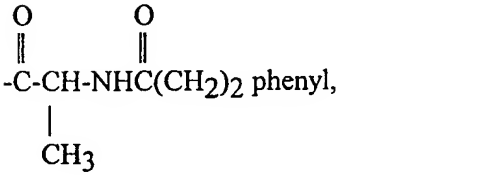


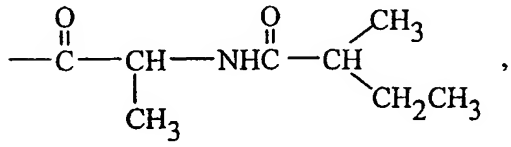


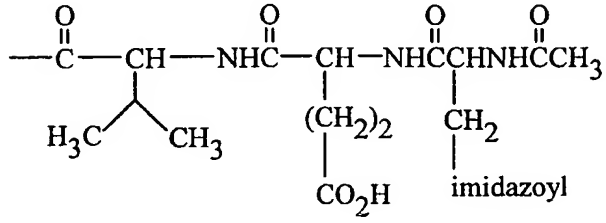


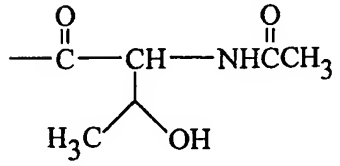


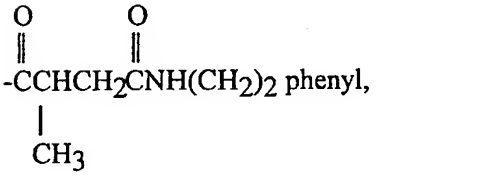


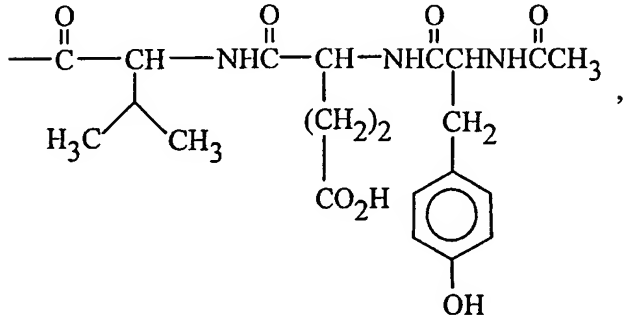


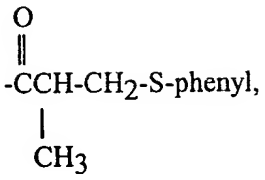


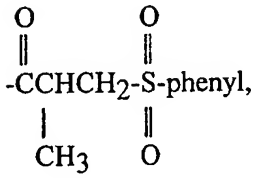


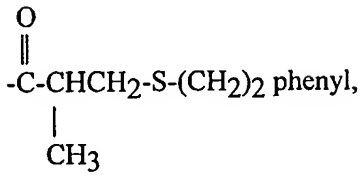


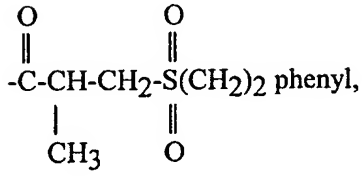


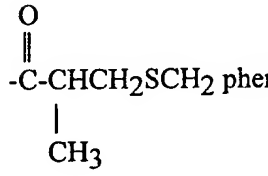


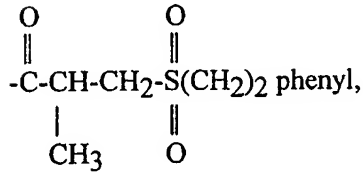


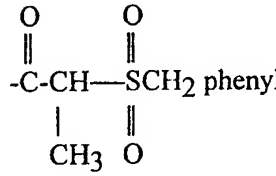


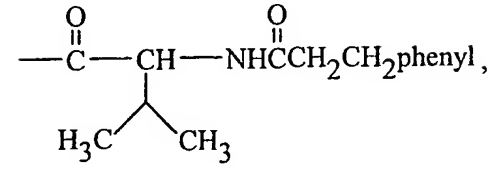


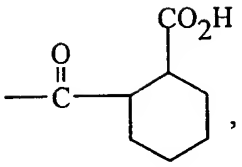


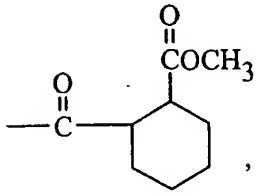


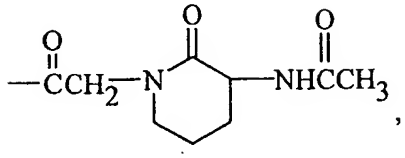


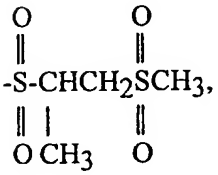


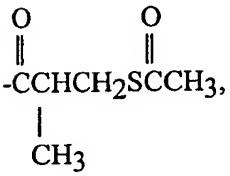


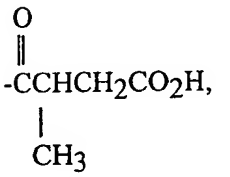


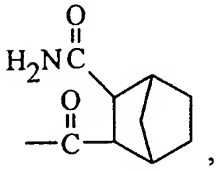


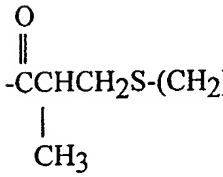


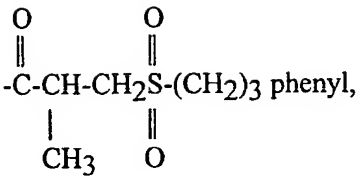


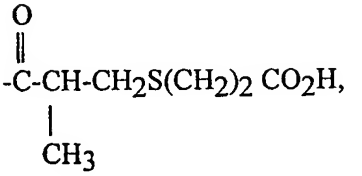


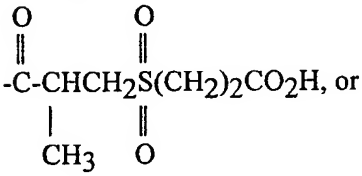


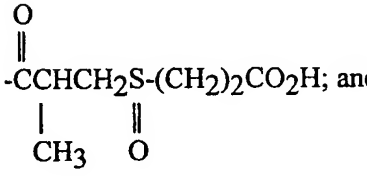












R^2 is

$-CH_2CH_2$ phenyl,

$-CH_2$ naphthyl,

$-CH_2CH_2$ cyclohexyl,

$-CH_2O$ naphthyl,

$-CH_2O$ phenyl,

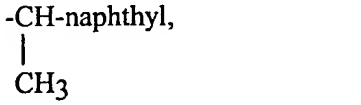
$-CH_2S$-phenyl,

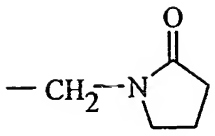
$-CH_2$-substituted naphthyl,

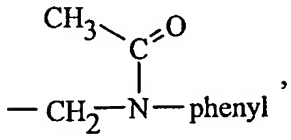
$-CH_2CH(phenyl)_2$,

$-CH_2$-imidazole,

$-(CH_2)_3$-phenyl,



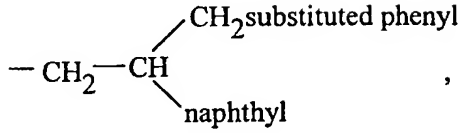




-CH[CH_2phenyl]$_2$,

-CH-naphthyl,
|
OH

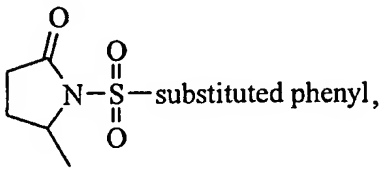
-CH_2-NH phenyl,

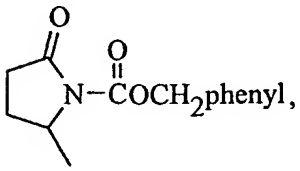


-CH_2-naphthyl-phenyl,

-CH_2-fluorenyl,

-CH_2 naphthyl-thienyl,



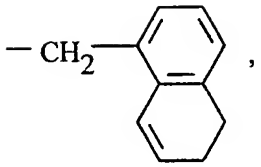


-CH_2-benzofuranyl,

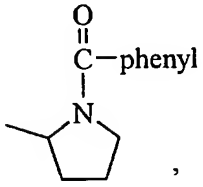
-CH_2-benzothienyl,

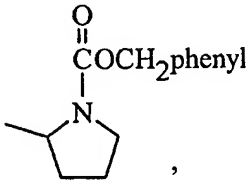
-CH_2-naphthyl-CH_2 phenyl,

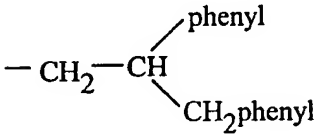
-CH_2-substituted phenyl,

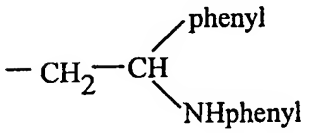


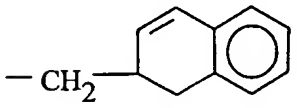
-CH_2-substituted indolyl,

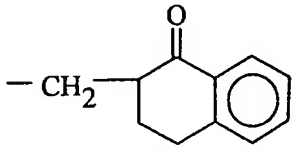


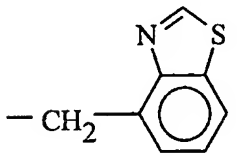


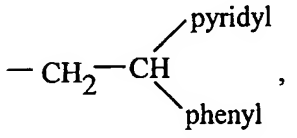


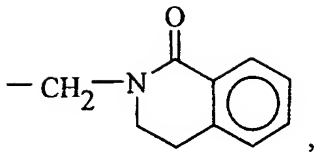






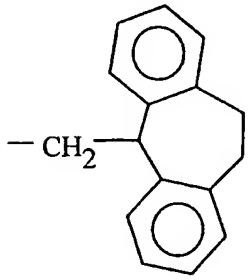






,

-$(CH_2)_2$ pyridyl, or



,

each n is independently 0 to 3, and the pharmaceutically acceptable, salts, esters, amides, and prodrugs thereof.

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/US 97/18514

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07C271/22 C07C233/47 C07C233/51 C07C311/19 C07D333/24

According to International Patent Classification(IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07C C07D

Documentation searched other than minimumdocumentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 618 223 A (SANDOZ) 5 October 1994 see claims 1,10; example 31 ---	1,30
X	ADNAN M.M. MJALLI ET AL : "Inhibition of interleukin-1beta converting enzyme by N-acyl-aspartic acid ketones" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, vol. 5, no. 13, 1995, pages 1405-1408, XP002053982 see page 1405; examples 3J-N ---	1,30
X	ADNAN M.M. MJALLI ET AL: "Activated ketones as potent reversible inhibitors of interleukin-1beta converting enzyme" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, vol. 4, no. 16, 1994, pages 1965-1968, XP002054017 see page 1965; example 4C --- -/--	1,30

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publicationdate of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

4

Date of the actual completion of theinternational search	Date of mailing of the international search report
30 January 1998	19. 02. 98

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Voyiazoglou, D

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/US 97/18514

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 623 592 A (STERLING) 9 November 1994 see claims 1,3 -----	1,30,43

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 97/ 18514

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 21-29
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim(s) 21-29 is(are) directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.: 1-18, 20, 30
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
The claims are so broad that to determining the scope of a meaningful search due account has been taken of Rule 33.3 PCT, special emphasis was put on the subject matter of claims 19, 31-40, 43 .

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte. onal Application No
PCT/US 97/18514

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 618223 A	05-10-94	CA 2117121 A	09-09-94
		JP 6340691 A	13-12-94
EP 623592 A	09-11-94	AU 676887 B	27-03-97
		AU 6075294 A	03-11-94
		CA 2122227 A	30-10-94
		CZ 9401035 A	16-11-94
		FI 942005 A	30-10-94
		HU 68563 A	28-06-95
		JP 7025865 A	27-01-95
		NO 941580 A	31-10-94
		NZ 260410 A	25-06-96
		SK 50294 A	08-02-95

CORRECTED VERSION*

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
C07C 271/22, 233/47, 233/51, 311/19, C07D 333/24

A1

(11) International Publication Number: **WO 98/16502**

(43) International Publication Date: 23 April 1998 (23.04.98)

(21) International Application Number: PCT/US97/18514

(22) International Filing Date: 9 October 1997 (09.10.97)

(30) Priority Data:
60/028,322 11 October 1996 (11.10.96) US

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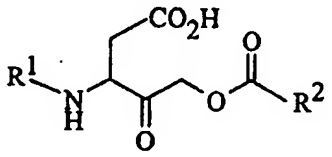

(I)

(57) Abstract

The present invention relates to compounds that are inhibitors of interleukin-1β converting enzyme that have formula (I). This invention also relates to a method of treatment of stroke, inflammatory diseases, reperfusion injury, Alzheimer's disease, and shigellosis, and to a pharmaceutically acceptable composition that contains a compound that is an inhibitor of interleukin-1β converting enzyme.

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